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MORRISON & FOERSTER LLP
12531 HIGH BLUFF DRIVE
SUITE 100
SAN DIEGO, CA 92130-2040

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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Application Number: 08/105,444

Filing Date: August 11, 1993

Appellant(s): SPITLER and MAIDA

Laurie L. Hill
For Appellant

EXAMINER'S ANSWER

This is response to appellant's Brief on appeal, filed 2/17/04.

The text of those sections of Title 35 U.S. Code not included in this appeal can be found in a previous Office Action herein.

Given the length of the Examiner's Answer, it is noted that the font and line spacing of the **Rejections** differ from the **Rebuttal to Appellant's Arguments** in the interest of limiting the size of the Office Action.

The examiner apologizes for any inconvenience to appellant and the BPAI in this matter. If desired, a copy of this Examiner's Answer all in the same font and line spacing will be provided upon request. No problemo.

(1) Real Party of Interest.

A statement identifying the real party of interest in contained in the Brief.

(2) Related Appeals and Interferences Identified.

At the time the Brief on Appeal was filed, a statement identifying the related appeal in then copending USSN 09/300,978, which would directly affect or would be directly affected by or would have a bearing on the decision in the pending appeal was contained in the Brief.

Subsequently, in the Reply to Notice of Non-Compliant Brief, filed 7/29/05;

appellant provided a copy of the Decision rendered by the BPAI in USSN 09/300,978 (Decision).

The Decision on Appeal in USSN 09/300,978 found that:

"Thus, we find no error in the examiner's conclusion that the subject matter of claim 13 on appeal as a whole would have been obvious to a person of ordinary skill in the art the time the invention was made."

See page 8, paragraph 3 of the Decision in USSN 09/300,978.

"Appellants' arguments overlook the broader disclosure in Spitler of using TAAs (tumor associated antigens) in general."

See pages 8-9, overlapping paragraph of the Decision in USSN 09/300,978.

"It is equally clear that immunotherapy of prostatic cancer based upon PSMA would be specific to prostatic tissue whether normal or malignant as discussed in Horoszewicz and Israeli."

See pages 9-10, overlapping paragraph of the Decision in USSN 09/300,978.

"Contrary to appellant's arguments, a joint reading of Spitler, Horoszewicz and Israeli shows that PSMA would be a desirable target."

See page 10, paragraph 2 of the Decision in USSN 09/300,978.

In making arguments concerning that the combination of references relied upon by the examiner was improper,

"appellants do not come to grips with the fact that Spitler itself states that use of an antigen or anti-ids to the antigen will be useful in those vaccine composition."

See page 10, paragraph 3 of the Decision in USSN 09/300,978.

"The decision of the examiner is affirmed."

See page 11, paragraph 3 of the Decision in USSN 09/300,978.

Appellant's statement, filed 7/25/05, that a copy of the Decision in USSN 09/300,978 was included merely for the convenience of the examiner is acknowledged.

Appellant statement, filed 7/25/05, that the consideration of the Decision in USSN 09/300,978 will be addressed as appropriate in the Reply Brief to the Examiner's Answer is acknowledged.

Further, it is noted that appellant did not provide their Request for Rehearing Pursuant to 37 CFR 1.97(b), filed 2/22/05, in USSN 09/300,978, nor has appellant provided the Decision On The Request for Rehearing, which denied the request for rehearing, mailed 4/25/05.

"We have considered the request for rehearing but the arguments presented are intimately tied to and rely upon Exhibit A – Exhibit D and thus are untimely and inappropriate. We do not find that the request for rehearing points to any argument set forth in the Appeal Brief or the Reply Brief, that we overlooked or misapprehended in reaching our decision of December 22, 2004."

See pages 2-3 of the On Request For Rehearing, mailed 4/25/05.

(3) Status of Claims.

The statement of the status of claims contained in the Brief is correct.

This appeal involves claims 1-14 and 21-40.

Claims 15-20 have been canceled previously.

(4) Status of Amendments After Final.

The appellant's statement of the status of amendments after final rejection contained in the Brief is correct.

(5) Summary of Invention.

The summary of invention contained in the Brief is substantially correct.

However, in contrast to appellant's assertions that there was no suggestion that antigens "over represented on normal prostate tissue can be used to elicit a protective therapeutic immune response against prostate cancer",

the prior art did recognize generating immune responses against tumor associated antigens, which encompasses antigens that are expressed on malignant and normal cells, including the induction of active immunity to prostate specific antigens (e.g. PSMA) at the time the invention was made.

Also, as pointed out above in the Section on **Related Appeals and Interferences Identified**,

The BPAI has affirmed the examiner's prior art rejection under 35 USC 103(a) in USSN 09/300,978, which directly affects and has a bearing on the decision on the pending appeal in the instant application USSN 08/105,444.

See the **Law of the Case** and the **Rebuttal** to the prior art rejection below.

(6) Issues.

Appellant's statement of the issues in the Brief is substantially correct.

It is noted that the enablement and written description rejections under 35 USC 112, first paragraph are directed against the recitation of "over represented prostate antigen" and "immunologically effective portions thereof" and not against full-length PSA, PAP and PSMA.

Also, it is noted that the prior art rejection of record appears to be directed against PSMA only.

The prior art teaches methods of treating prostate cancer and prostate cancer vaccines as they read on PSMA and reads on all of the pending claims.

However, the record does not show that either a Restriction or an election of species requirement was made in the instant application.

Appellant is invited to clarify the record by indicating whether a species election had been made during the prosecution of this application for prior art purposes.

(7) Grouping of Claims.

Appellant's submission that the case law seems to suggest differing standards in assessing the patentability of method and composition claims is acknowledged.

While appellant maintains the claimed inventions of both groups of claims (Group I, drawn to claims 1-7 and methods of eliciting antitumor immune responses and Group II, drawn to claims 8-14 and 21-40 and vaccines) are patentable,

the examiner maintains that the claims are not patentable for the reasons of record and addressed herein.

(8) Claims Appealed.

The copy of the appealed claims contained in the Appendix to the Brief is correct.

(9) Art of Record.

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

(A) Andriole et al., Ann. Rev. Med. 42: 9-15, 1991.

(B) Arlen et al. Current Opinion in Investigational Drugs 6: 592-596, 2005.

(C) Ezzell, J. NIH Research 7: 46-49, 1995.

(D) Hanks et al., Chapter 35, Cancer of the Prostate on pages 1073-1113 of Cancer Principles & Practice of Oncology, 4th Edition, edited by DeVita et al., J.B. Lippincott Company, Philadelphia.

(E) Harris et al., Seminars in Oncology 26: 439-447, 1999.

(F) Hodge et al., Int. J. Cancer 63: 231-237, 1995.

(G) Horoszewicz, U.S. Patent No. 5,162,504.

(H) Hwang et al., Seminars in Oncology 26: 192-201, 1999.

(I) Israeli et al., U.S. Patent No. 5,538,866.

(J) Kuby, Immunology, Second Edition, W.H. Freeman and Company, New York, 1991; see page 590, column 2 and page 613, column 2; Tumor-Associated Antigens and Tumor-Specific Antigens.

(K) McCarley et al., Seminars in Surgical Oncology 5:293-301, 1989.

(L) McNeel et al., Immunology Letters 96: 3-9, 2005.

(M) Meidenbauer et al., The Prostate 43 : 88-100, 2000.

(N) Paul, (Ed), Fundamental Immunology, Second Edition, Raven Press, New York, 1989; see page 931, column 1, paragraph 1; Differentiation Antigens and Other Tumor-Associated Antigens.

(O) Peshwa et al., The Prostate 36: 129-138, 1998.

(P) Salgaller, Peptides in Prostate Cancer (see Peptide – Based Cancer Vaccines, edited by Kast, published by Landes Bioscience, 2000; see Chapter 10, pages 155-171.

(Q) Spitler, U.S. Patent No. 5,738,867.

(R) Spitler, Cancer Biotherapy 10:1-3, 1995.

(S) Xu et al., Cancer Research 60 : 1677 – 1682, 2000.

(T) Webster's Ninth New Collegiate Dictionary, Merriam-Webster Inc., Springfield, MA, 1990; see pages 1176 and 1290.

(U) Wright, U.S. Patent No. 5,227,471.

For the convenience of the BPAI, the following references cited by appellant via the Spitler Declaration are provided for completing the instant file application. Complete copies of each of the references do not appear in the scanned instant filed application.

(V) Barth et al., Cancer Research 54: 3342-3345, 1994.

(W) Berd et al., J. Clin. Oncol. 15: 2359-2370, 1997.

(X) Bystryn et al., Cancer 69: 1157-1164, 1992.

(Y) McCune et al., Cancer Immunol. Immunother. 32: 62-66, 1990.

In addition, **the Decisions by the BPAI from USSN 09/300,978** are provided as well.

(Z) Decision on Appeal. Appeal No. 2004-1185, Application No. 09/300,978, mailed 12/22/04.

(AA) On Request For Rehearing, Appeal No. 2004-1185, Application No. 09/300,978, mailed 4/25/05.

(10) Grounds of Rejection.

Again, it is noted that the font and line spacing of the **Rejections** differ from the **Rebuttal to Appellant's Arguments** in the interest of limiting the size of the Office Action.

The following ground(s) of rejection are applicable to the appealed claims.

Rejection Under 35 U.S.C. § 112, First Paragraph, Written Description

Claims 1-14 and 21-40 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are drawn to methods of eliciting anti-tumor responses to prostate tumors by administering:
A) "at least one antigen over represented in the prostate gland or an immunologically effective portion thereof" (e.g., see claim 1);
B) "an expression system capable of generating in situ said antigen" (e.g., see claim 1), and
C) wherein said antigen is a "protein" or a "peptide" (e.g., see claim 2).

Such "over represented antigens", "expression system (comprising encoding nucleic acid or DNA sequences)", "proteins" and "peptides" do not meet the written description provision of 35 USC 112, first paragraph. There is insufficient guidance and direction as to the written description of these "over represented antigens", "expression systems comprising encoding nucleic acid or DNA sequences", "proteins" and "peptides".

The specification as filed discloses that the antigen may be a protein or a peptide, or peptide fragment of the protein, or may be a carbohydrate, glycoprotein, lipoprotein or lipid".
See page 6, paragraph 1 of the instant specification.

While the instant specification discloses PSA, PAP and PSMA as known antigens which are over represented on prostate, "the invention includes any other antigens substantially uniquely present on the prostate gland so that the prostate derived tissue can be distinguished from other tissue by virtue of the presence of these antigens".
See Illustrative Antigens on pages 7-10, particularly pages 9-10, overlapping paragraph of the instant specification.

Neither the specification as filed nor appellant have provided sufficient description of known "over represented prostate antigens", including any "protein or a peptide, or peptide fragment of the protein, or may be a carbohydrate, glycoprotein, lipoprotein or lipid" other than those known prostate antigens at the time the invention was made, namely PSA, PAP and PSMA.

At the time the invention was made,
Cancer Principles & Practice of Oncology, 4th Edition, edited by DeVita et al., J.B. Lippincott Company, Philadelphia, 1993 (See Chapter 35, Cancer of the Prostate on pages 1073 – 1113 by Hanks et al.) (Hanks et al.) notes that:
"The two markers of proved clinical utility in the diagnosis and management of carcinoma of the prostate were measurement of levels of PAP and PSA.:
See Markers of the Prostate Cancer on pages 1079-1081 of Hanks et al.

"PAP and PSA are subject to the general constraint for all tumor markers. First, no tumor marker is expressed consistently. PAP and PSA are expressed less in poorly differentiated than in well-differentiated tumor. Histochemical studies typically reveal considerable variation in the expression of both markers from cell to cell within a tumor mass. ... All the factors listed above lead to considerable patient-to-patient variability in marker elevation associated with any given clinical stage and render markers inaccurate staging tools. Finally the correlation between shrinkage of tumor mass and the decline of a marker is not straightforward."
See page 1080, column 1, paragraph 1 of Hanks et al.

"Tumors arising from these cells can manifest PSA- and PAP-positive bladder tumors and PSA-negative PAP-positive rectal carcinoids. In addition, normal axillary and perineal apocrine sweat glands, some apocrine foci in fibrocystic breast disease and apocrine sweat gland carcinomas may stain positive with polyclonal, but not monoclonal anti-PSA antibody. There is a single report of a PSA-producing small cell carcinoma of unknown primary."
See pages 1080-1081, overlapping paragraph of Hanks et al.

In further evidence of the absence of possession of the "genus limitations" indicated above as well as the limited number of over represented prostate antigens at the time the invention was made, the following is noted.

About six (6) years subsequent to applicant's filing date of 8/11/93,
Hwang et al. (Seminars in Oncology 26: 192-201 (1999) (Hwang et al.) discuss Prostate Cancer Vaccines: Current Status (see entire document) by stating:

"The paucity of antigens known to be specific for prostate cancer has been a major obstacle to the development of antigen-specific vaccines. The most extensively studied antigens have been PSA and PSMA."
See pages 197-198, overlapping paragraph of Hwang et al.

"While PSA and PSMA have both been shown to stimulate an immune response in vitro, they represent only our "best guess" and may not be true prostate cancer-rejection antigens. An antigen's prevalence, ability to activate T cells and the relative abundance of TCRs specific for each antigen/ MHC complex may define an antigen's ability to prime an immune response. Abundant and potent antigens such as bacterial and viral antigens are thought to hide more "cryptic" antigens, such as tumor and normal tissue antigens. Identification of these true tumor-rejection antigens could provide an avenue for more potent antitumor immunity".
See page 198, column 1, paragraph 2 of Hwang et al.

Similarly, six (6) years later in a reference co-authored by co-inventor Spitler,
in Harris et al., Seminars in Oncology 26: 439 – 447 (1999) (Harris et al.), indicates that:
PSA, PSMA and PAP were the only targets described that have been identified that could serve as targets for an immune response.
See page 439, column 1, paragraph 2 of Harris et al.

It is noted that Harris et al. refers back to the Hwang et al., Seminars in Oncology reference above as a review of the current status of prostate cancer vaccines.
See page 439, column 2, paragraph 1 of Harris et al. as reference (7).

Therefore, it appears that the PSA, PAP and PSMA were the identified prostate antigens that could serve as targets for an immune response in immunological approaches to the treatment of prostate cancer in the art at the time the invention was made and as well as art about six (6) years subsequent to applicant's filing date of 8/11/93.

Further in the year 2000, seven (7) years subsequent to the filing date of the instant application,
Xu et al. (Cancer Research 60 : 1677 – 1682, 2000) note that the reported prostate markers PAP, PSMA, prostate inhibin peptide, PCA-1, PR92, prostate-associated glycoprotein complex, prostate mucin antigen 12-lipoxygenase and p53 "are not entirely tissue and/or cancer specific, hence improved markers are needed for the diagnosis, prognosis and therapy of prostate cancer".
See Introduction of Xu et al.

In addition, Xu et al. note that "numerous approaches have been used to dissect the genetic composition of prostate and prostate cancer and that none of the known techniques have provided a complete, systematic and reliable comparison of gene expression between tissue types. Expression cloning using cancer patient serum or T cell lines or clones form patients have identified a panel of genes that may be immunologically relevant, although none have yet been validated and the process is not very efficient."
See Introduction of Xu et al.

In addition with respect to the claimed limitations of "at least one antigen over represented in the prostate gland and immunologically effective portion thereof" as well as "proteins" and "peptides, the following is noted.

Salgaller describes Peptides in Prostate Cancer (see Peptide – Based Cancer Vaccines, edited by Kast, published by Landes Bioscience, 2000; see Chapter 10, pages 155 – 171) (Sallager) by noting the following.

As far as peptide targets of prostatic carcinoma immunotherapy are concerned, the majority of the clinically applied investigations to date (i.e. the year 2000, seven (7) years subsequent to applicant's filing date) have centered on four proteins: PAP, PSA, PSMA and MUC-1.
See page 156, paragraph 1) of Salgaller.

In reviewing the work of Peshwa et al. (of record), the selection of candidate peptides that were predictive to be HLA-2 binders were selected and one was chosen for additional study. However, this peptide was weakly immunogenic in vitro, resulted in moderate cytotoxicity at best and recognition of endogenously synthesized PAP was not strong. "The low level of immunogenicity likely reflects the biological reality of the molecule rather than any deficiency with the assay system employed."
See page 157, paragraphs 2-3 of Salgaller.

"So as to develop a peptide-based immunotherapy approach, the amino acid sequence of PSA was studied for peptide motifs most likely to bind to HLA-A2."
See page 158, paragraph 2 of Salgaller.

"At first glance it might be disconcerting that so much effort was required to generate what turned out to be a low frequency of in vitro immune reactivity. Yet there is no conclusive data that immunogenicity in vitro strongly correlates with clinical benefit in vivo. In fact, it is interesting that the melanoma antigen MART-1/ MelanA is potently immunogenic in vitro. And yet has produce disappointing clinical results."
See page 160, paragraph 1 of Salgaller.

"Interestingly, the future direction of many antigen-based prostate cancer vaccines involves the use of proteins rather than peptides."
See Future Directions on pages 166—167 of Salgaller.

Therefore, the facts indicate that the PSA, PAP and PSMA were the identified "prostate antigens" that could serve as targets for an immune response in immunological approaches to the treatment of prostate cancer in the art at the time the invention was made and as well as in the art about six (6) years subsequent to applicant's filing date of 8/11/93 (e.g., see page 439, column 1, paragraph 2 of Harris et al.).

To this date, appellant has not provided sufficient direction either to the specification as filed or to the art of the "description or identifying characteristics" of the structure of the "over represented prostate antigens" broadly encompassing any "over represented prostate antigen", "expression system (comprising encoding nucleic acid or DNA sequences)", "proteins" and "peptides" as claimed and
that the "over represented antigen" may be a protein or a peptide, or peptide fragment of the protein, or may be a carbohydrate, glycoprotein, lipoprotein or lipid",
other than full-length PSA, PAP and PSMA.

As the evidence indicates,
appellant was not in the possession of a genus of "over represented prostate antigens", other than full-length PSA, PAP and PSMA;
and even with the disclosure of additional prostate antigens seven (7) years subsequent to the 1993 filing date of the instant application, the skilled artisan recognized that these prostate antigens were not entirely tissue and/or cancer specific and
that improved markers were still needed for the diagnosis, prognosis and therapy of prostate cancer.

The instant disclosure as filed did not provide even for one working example of either "a peptide, or peptide fragment of the protein" (including an immunologically effective portion of PSA, PAP or PSMA), as well as "a carbohydrate, glycoprotein (other than full-length PSA, PAP and PSMA), lipoprotein or lipid".

Given that the structures of PSA, PAP and PSMA are unique and each would be expected to have its own constraints on appropriate "immunologically effective portions and peptides" that met the claimed limitations and given the lack of correlation between even appropriate candidate peptides and their ability to generate in vitro / in vivo antitumor immune responses,
the skilled artisan would have recognized that appellant was not in possession of sufficient information for the correlation between the structure and function or the sufficiently detailed relevant identifying characteristics between the structure between the structure and function
by which a person of ordinary skill in the art would understand that the inventors possessed the claimed invention encompassing "over represented prostate antigens" and "immunologically effective portions and peptides", other than PSA, PAP and PSMA.

Appellant has not provided sufficient objective evidence that the skilled artisan would be able to identify the claimed "over represented antigens" by a mere assertion or description of a class of over represented prostate antigens that are expressed almost exclusively, i.e. substantially uniquely, on normal prostate tissue at such a level that an immune response elicited against that antigen results in the simultaneous elimination of normal and malignant prostate tissue,
other than simply disclosing that the necessary common attribute of these over represented prostate antigens is that they are "overrepresented on normal prostate tissue while also being expressed on malignant prostate tissue" and, in turn,
that they can generate effective antitumor immune response in the prevention and treatment of prostate cancer.

An alleged conception having no more specificity than that it is simply a wish to know the identity of any material with that biological property.

Appellant is reminded of their own disclosure and statements concerning the emerging and unpredictable technology or invention of providing cancer vaccines.

As disclosed on page 2, paragraph 1 of the instant specification;
appellant discloses that prostate cancer continues to be refractory to treatment despite many years of efforts to improve therapy. Similarly, appellant discloses that at the time the invention was made; vaccine development has been slow and no vaccine approved by the FDA for marketing currently exists for any form of cancer.

As the instant co-inventor Spitler acknowledges,
"Ask practicing oncologists what they think about cancer vaccines and you're likely to get the following response: "cancer vaccines don't work". Ask a venture capitalist or the director of product development at a large pharmaceutical company, and you're likely to get the same response".
See Spitler, Cancer Biotherapy 10:1-3, 1995; page 1, column 1, paragraph 1.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483.

Other than full-length PSA, PAP and PSMA prostate antigens, there is insufficient written description of the claimed "antigen over represented in the prostate gland or an immunologically effective portion thereof" broadly encompassed by the claimed invention. There is a lack of disclosure of sufficient relevant identifying characteristics coupled with a known or disclosed correlation between function and structure of the broadly diverse "over represented prostate antigens" and "immunologically effective portions thereof", including "peptides" and "proteins" recited in the claimed invention, other than the full-length PSA, PAP and PSMA prostate antigens, at the time the invention was made.

Given the distinctions between structure, function and expression between the known prostate antigens at the time the invention was made,

given the requirement of the structure of the protein and knowledge about HLA binding to determine appropriate peptides motifs to study for generating immune responses and amino acid differences,

given the lack of identification as well as correlation of such information to those peptides that would generate an antitumor immune responses in vivo even for the disclosed and known PAP, PSA and PSMA prostate antigens,

appellant has not provided a sufficient description showing possession of the necessary functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genuses of "over represented prostate antigens" or "immunologically effective portions thereof", "expression system (comprising encoding nucleic acid or DNA sequences)", "proteins" and "peptides", broadly encompassed by the claimed invention.

Further, the Court has interpreted 35 U.S.C. §112, first paragraph, to require the patent specification to "describe the claimed invention so that one skilled in the art can recognize what is claimed. Enzo Biochem, Inc. v. Gen-Probe Inc, 63 USPQ2d 1609 and 1618 (Fed. Cir. 2002). In evaluating whether a patentee has fulfilled this requirement, our standard is that the patent's "disclosure must allow one skilled in the art 'to visualize or recognize the identity of' the subject matter purportedly described." Id. (quoting Regents of Univ. of Cal. v. Eli Lilly & Co., 43 USPQ2d 1398 (Fed Cir. 1997)).

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species; then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3).

Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Appellants have been directed to Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday January 2001. Also, See MPEP 2163.

Rejection Under 35 U.S.C. § 112, First Paragraph, Enablement

Claims 1-14 and 21-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "full-length PSA, PSMA and PAP"; does not reasonably provide enablement for any
"over represented prostate specific antigen", "expression system (comprising encoding nucleic acid or DNA sequences) that generate said antigen or antigens in situ", "immunologically effective portion thereof", "protein" or "peptide".

The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention commensurate in scope with these claims.

Appellant has not provided sufficient biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies "over represented prostate antigens", "proteins" or "peptides". "expression system (comprising encoding nucleic acid or DNA sequences) that generate said antigen or antigens in situ", other than the known "PSA, PAP or PSMA" prostate antigens at the time the invention was made. While "over represented prostate antigen" and "immunologically effective portion thereof" may have some notion of the claimed active ingredients; there is insufficient direction and guidance which enables the skilled artisan to make and use "over represented prostate specific antigen" and "immunologically effective portion thereof", commensurate in scope with the claimed invention.

Appellant has not enabled the breadth of the claimed invention in view of the teachings of the specification. Factors to be considered in determining scope and enablement are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented in the specification, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breadth of the claims. See Ex parte Forman, 230 USPQ 546, BPAI, 1986.

Appellant has not disclosed how to make and use the claimed vaccines and methods to treat prostatic cancer as a therapeutic regimen in humans, as broadly encompassed by the claimed invention. There is insufficient evidence of the invention with respect to the in vivo operability of the claimed prostate-specific proteins, peptides or portions thereof and expression systems to use appellant's invention.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Concerning vaccines to elicit anti-tumor responses in general, the antigenic or immunogenic nature of a protein or expression system does not necessarily correlate with its ability to confer anti-tumor responses.

As disclosed on page 2, paragraph 1 of the instant specification, appellant discloses that:
"Prostate cancer continues to be refractory to treatment despite many years of efforts to improve therapy. Similarly, appellant discloses that at the time the invention was made; vaccine development has been slow and no vaccine approved by the FDA for marketing currently exists for any form of cancer."

As the instant co-inventor Spitler acknowledges,
"Ask practicing oncologists what they think about cancer vaccines and you're likely to get the following response: "cancer vaccines don't work". Ask a venture capitalist or the director of product development at a large pharmaceutical company, and you're likely to get the same response".
See Spitler, Cancer Biotherapy 10:1-3, 1995; page 1, column 1, paragraph 1.

Therefore, appellant has recognized the lack of predictability of the nature of the art and state of the prior art to which the instant invention pertains, as similarly disclosed on page 2 of the specification as-filed.

Appellant has not provided sufficient objective evidence that predicts the efficacy of the instant invention drawn to "over represented prostate antigens", "immunologically effective portions of PSA, PSMA or PAP", "expression systems", "proteins" and "peptides" in the specification as filed for the treatment or prevention of human prostatic cancer.

Also, such disclosures clearly indicate that the amount of direction or guidance presented in the specification is limited, and would not permit a person skilled in the art to use the invention without undue experimentation at the time the invention was made.

Cancer vaccines, including, Prostate Cancer Vaccines and Immunotherapy have been a highly unpredictable art which is amply supported by the evidence. It is important to realize that cancer vaccines, including prostate cancer vaccines and immunotherapy have not been straightforward or as easy to apply as was initially hoped, nor has the interpretation of results been unambiguous and has led to the dismissal in certain instances.

The amount of experimentation required to adapt the practice of prostate cancer immunotherapy has been quite high, with a number of failed attempts, including appellant's own efforts.

In the absence of objective evidence to the contrary, it appears that the PSA, PAP and PSMA were the identified prostate antigens that could serve as targets for an immune response in immunological approaches to the treatment of prostate cancer in the art at the time the invention was made and as well as art about six (6) years subsequent to applicant's filing date of 8/11/93.

"PAP and PSA are subject to the general constraint for all tumor markers. First, no tumor marker is expressed consistently. PAP and PSA are expressed less in poorly differentiated than in well-differentiated tumor. Histochemical studies typically reveal considerable variation in the expression of both markers from cell to cell within a tumor mass. ... All the factors listed above lead to considerable patient-to-patient variability in marker elevation associated with any given clinical stage and render markers inaccurate staging tools. Finally the correlation between shrinkage of tumor mass and the decline of a marker is not straightforward."
See page 1080, column 1, paragraph 1 of Hanks et al.

"The paucity of antigen known to be specific for prostate cancer has been a major obstacle to the development of antigen-specific vaccines. The most extensively studied antigens have been PSA and PSMA."
See pages 197-198, overlapping paragraph of Hwang et al.

"While PSA and PSMA have both been shown to stimulate an immune response in vitro, they represent only our "best guess" and may not be true prostate cancer-rejection antigens."
See page 198, column 1, paragraph 2 of Hwang et al.

Further in the year 2000, seven (7) years subsequent to the filing date of the instant application, Xu et al. note that the reported prostate markers PAP, PSMA, prostate inhibin peptide, PCA-1, PR92, prostate-associated glycoprotein complex, prostate mucin antigen 12-lipoxygenase and p53 are not entirely tissue and/or cancer specific, hence improved markers are needed for the diagnosis, prognosis and therapy of prostate cancer.
See Introduction of Xu et al.

In addition, Xu et al. note that numerous approaches have been used to dissect the genetic composition of prostate and prostate cancer and that none of the known techniques have provided a complete, systematic and reliable comparison of gene expression between tissue types. Expression cloning using cancer patient serum or T cell lines or clones form patients have identified a panel of genes that may be immunologically relevant, although none have yet been validated and the process is not very efficient.
See Introduction of Xu et al.

With respect to the predictability of immune responses and antitumor responses in prostate cancer, the following is noted.

"Knowledge of the immune response to prostate cancer has been extremely limited."
See page 193, column 1, first full paragraph of Hwang et al.

"It is important to be aware that immune responses to vaccination do not necessarily imply that the response elicited is against an immunogenic tumor antigen. Furthermore, the magnitude of decreases in PSA levels may not correlate with a clinically meaningful outcome."
See page 593, paragraph 1 of Arlen et al.

"Interestingly, the future direction of many antigen-directed prostate cancer vaccines involves the use of proteins rather than peptides. Proteins as targets of immunotherapy have several advantages over peptide-based therapeutics including, but not limited to: 1) lack of severe HLA haplotype restrictions (thus making treatment immediately relevant to a larger patient populations), 2) potential helper and adjuvant epitope effects, and 3) lack of need to define the target antigen(s). However, the disadvantages of abandoning peptide-based immunotherapeutics cannot be discounted. The possibility of generating immune responses to dominant, but clinically irrelevant, heterologous epitopes is one of the major drawbacks."
See page 166, second full paragraph 2 of Salgaller. See Future Directions.

"Once an overexpressed protein is detected, and its frequency across and within tumor types is established, it appears as though most laboratories are choosing protein-based cancer vaccine as their initial clinical approach. This is most likely because of the difficulty in defining the precise epitopes responsible for immunogenicity. The technologies required to define such epitopes, among them tandem mass spectroscopy, are much more difficult and time-consuming than histologically based techniques."
See page 166, paragraph 3 of Salgaller. See Future Directions.

"As methodologies for the molecular profiling of tumor genes becomes more efficient, e.g. using differential display and microarray analysis, putative markers for prostate cancer have been put forth. It is crucial that the potential immunogenicity of such genes has been established as early as possible. It is counterproductive to initiate a comprehensive study of a gene whose overespression may be irrelevant to cancer."
See page 166, paragraph 4 of Salgaller.

"The development of antigen-specific therapies is hampered by the paucity of information concerning prostate cancer immunology, including the identification, abundance and immunodominance of tumor-associated or –specific prostate cancer epitopes."
"Yet, especially when compared to other carcinomas, much work needs to be done in the realm of understanding the relationship between the immune system and prostate cancer."
See page 167, paragraph 2 of the Salgaller.

The goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual disease. Ezzell reviews the current thinking in cancer vaccines and states that tumor immunologists are reluctant to place bets on which cancer vaccine approach will prove effective in the long run (J. NIH Research 7: 46-49, 1995; see entire document, particularly the last paragraph; 1449). It has been well known in the art that tumor cells in vivo simply do not display their unique antigens in ways that are easily recognized by cytotoxic T lymphocytes (Ezzell; page 48, column 2, paragraph 2). Furthermore, no one is very optimistic that a single peptide or a virus carrying the gene encoding that peptide will trigger an immune response strong enough to eradicate tumors or even to prevent the later growth of micrometastases among patients whose tumors have been surgically removed or killed by radiation or chemotherapy (Ezzell; page 48, paragraph 6).

Furthermore, Hodge et al. (Int. J. Cancer 63: 231-237, 1995; 1449) discloses that previous attempts to actively immunize patients with prostate adenocarcinoma cells admixed with adjuvant shown little or no therapeutic benefit (page 231, column 1, first paragraph of Introduction). Here, the reference discloses that these previous attempts to actively immunize were known in 1990, prior to appellant's invention. Such prostate adenocarcinoma cells and normal prostate cells express common antigens. Therefore, targeting prostate-specific antigens that are expressed on both normal and tumor cells in cancer immunotherapy to target tissue-specific antigens was known and practiced at the time the invention was made.

With respect to prostate-specific immunotherapy, Hodge et al. (Int. J. Cancer, 1995; 1449) discloses that previous attempts to actively immunize patients with prostate adenocarcinoma cells admixed with adjuvant shown little or no therapeutic benefit (page 231, column 1, first paragraph of Introduction). Models of evaluation of prostate therapeutics including the canine and the Dunning rat are not practical for PSA-recombinant vaccines due to the very low homology of rat and canine PSA to human PSA (page 231, column 2, paragraph 2). The fact that human PSA is a secreted antigen should be taken into consideration for its potential use as a target for human prostate cancer, as the secreted antigen may also reduce immunoglobulin responses by forming antigen-antibody complexes and/or potentially anergizing specific T cell responses (page 235, column 1, lines 1-6). An immune reaction directed against PSA could lead to side effects resulting from cross-reactivity with other kallikrein family members (page 235, column 2, lines 4-6). Therefore, the use of prostate-specific antigens in vaccines are likely to be limited by either neutralization by secreted prostate antigen or by inducing autoimmunity. Although the recombinant human PSA construct was unable to elicit an anti-PSA IgG response, PSA-specific IgM response were noted in all immunized monkeys (page 236, column 1, paragraph 1). However, these antibody responses were of low titer, were short-lived and could not be boosted. It is noted that the monkeys developed in vitro lymphoproliferative responses to PSA (page 236, column 1, paragraph 2). However, it is not clear that such studies can be extrapolated to humans because in the difference in MHC motifs between rhesus and humans and the levels of expression of class I and II MHC on rhesus vs. human prostate and human normal prostate vs. prostate carcinoma (page 236, column 2, last paragraph). In addition to these cautions with respect to appropriate antigen presentation and subsequent immune responses (issue of MHC), this reference clearly indicates limited antibody responses and only some level in vitro cellular immunity with prostate specific antigen immunization. Also, this reference clearly indicates the limitations of animal models in prostate cancer modalities and that previous attempts at human prostate cancer vaccination with whole cells.

With respect to inducing prostate tumor-specific cytotoxic T lymphocytes; Peshwa et al. (The Prostate 36: 129-138, 1998) discloses that the protein sequence of PAP was evaluated using an algorithm to detect contiguous 9-amino acid peptides stretches which could potentially bind the HLA-A2 molecule; that various binding affinities were noted among the tested peptides, resulting in PAP-5 epitope as the most relevant for PAP-based therapeutic vaccines for prostate cancer (see Results); and that of the five nonapeptides shown to exhibit strong binding affinity for the HLA-A2 molecules, only PAP-5 is contained with the mature secreted PAP protein (page 136, column 1, paragraph 1).

While page 12 of the specification discloses screening for identifying peptides which may be important epitopes generally; appellant has not provided sufficient direction and guidance nor objective evidence in identifying or identification with "immunologically effective portions" of "over represented prostate antigens, including PSA, PSMA, PAP".

While Peshwa et al. (The Prostate, 1998) discloses that similar approaches employing dendritic cells loaded with HLA-A2 binding peptides of PSMA have been reported to have a clinical benefit (see Discussion); it appears that undue experimentation would be required of one skilled in the art to practice the claimed methods and compositions in providing effective vaccines for prostatic cancer using the teaching of the specification alone.

Insufficient direction or guidance is provided to assist one skilled in the art in the selection of all such possible "over represented antigens" and/or "immunologically effective portions thereof, including PSA, PSMA and PAP" nor is there sufficient objective evidence provided that all such "antigens" and "immunologically effective portions thereof" would be suffiicient to stimulate anti-tumor responses .

The specification does not provide a sufficient enabling description of the claimed invention. There is insufficient direction and guidance to enable a skilled artisan to make and use "over represented antigens", "immunologically effective portions thereof", "proteins" and "expression systems", as recited in the claims. A person of skill in the art would not know which "over represented antigens", "immunologically effective portions of said over represented antigens, including PSA, PAP, and PSMA", "proteins" and "peptides" are essential or effective to stimulate anti-tumor responses, which "antigens"/ "portions thereof" are non-essential or noneffective, and what particular lengths identify essential or effective portions. The problem of predicting polypeptide structure from mere sequence data of limited full length prostate antigens sequences and, in turn, utilizing predicted structural determinations to ascertain immunologically effectivel portions of over represented prostate antigens and finally what changes can be tolerated with respect thereto and, in turn, which stimulate anti-tumor responses is complex and well outside the realm of routine experimentation

In reviewing the work of Peshwa et al. (of record), the selection of candidate peptides that were predictive to be HLA-2 binders were selected and one was chosen for additional study. However, this peptide was weakly immunogenic in vitro, result in moderate cytotoxicity at best and recognition of endogenously synthesized PAP was not strong. The low level of immunogenicity likely reflects the biological reality of the molecule rather than any deficiency with the assay system employed.
See page 157, paragraphs 2-3 of Salgaller.

At first glance it might be disconcerting that so much effort was required to generate what turned out to be a low frequency of in vitro immune reactivity. Yet there is no conclusive data that immunogenicity in vitro strongly correlates with clinical benefit in vivo. In fact, it is interesting that the melanoma antigen MART-1/ MelanA is potently immunogenic in vitro. And yet has produce disappointing clinical results.
See page 160, paragraph 1 of Salgaller.

In addition, these published peer-reviewed reports and observations concerning the lack of predictability of inducing antitumor immune responses to any "over represented prostate antigen" or "immunologically effective portion thereof" in the published literature is consistent with appellant's own disclosure and statements concerning the emerging and unpredictable technology or invention of providing cancer vaccines.

Furthermore, these published peer-reviewed reports and observations concerning the lack of predictability of inducing prostate tumor immune responses is consistent with the failure of appellant's own clinical trials in providing a clinical benefit to the OncoVaxP™ vaccine, relied upon by appellant to provide sufficient enablement for the breadth of the claimed invention.

In Meidenbauer et al., (The Prostate 43 : 88-100, 2000) (Meidenbauer et al.) (and co-authored by co-inventor Spitler), the following observations were made.

"In contrast to the positive ELISPOT assays, we were unable to detect any killing of PSA-pulsed target in ^{51}Cr-release assays."

"Additionally, our date suggest that PSA-specific T cells consists to a large extent of $CD4^+$ T cells which may not have strong cytolytic activity."

"We report here, for the first time, that a PSA-based vaccine can generate cellular responses. Most the response were sustained but at a low level, and in vitro sensitization was necessary to be able to detect postvaccination changes in the frequency of PSA-reactive T cells in ELISPOT assays.

"Due to the small size of our pilot studies, no firm conclusions about the clinical efficacy of these treatments are possible."

"It appears that larger studies are warranted to assess the clinical benefit of the vaccine in patients with prostate cancer and to correlate the clinical outcome with immunological endpoints, such as frequency of PSA-responsive T cells."

See Discussion, particularly page 98, column 2, paragraph 1-2 of Meidenbauer et al.

In McNeel et al. (Immunology Letters 96: 3-9, 2005) (McNeel et al.), the following was noted.

"Spitler and coworkers reported the generation of PSA-specific $CD4^+$ T cells in some subjects treated. No clinical benefit was described, however, and this approach is not being further pursued"

See Protein-based vaccines on page 5, column 1 of McNeel et al.

The amount of direction presented and the lack of working examples provided in the application as filed is very narrow despite the wide breadth of the claims at issue, the unpredictability of prostate cancer immunotherapy and the high quantity of experimentation necessary to practice the breadth of claims.

Other than full-length PSA, PAP and PSMA prostate antigens, there is insufficient through illustrative examples or terminology to teach those how to make and use the claimed "antigens over represented in the prostate gland or an immunologically effective portions thereof" as broadly encompassed by the claimed invention.

As page 9, paragraph 3 of the instant specification discloses that:

"the invention includes any other antigens that substantially uniquely present on the prostate gland so that prostate derived tissues can be distinguished from other tissue by virtue of the presence of these antigens",

and as page 10, paragraph 1 of the instant specification discloses that:

"antigens useful in the vaccines may be prepared by any suitable methods".

As pages 11-12 of the instant specification discloses:

"Similarly, it may be desirable to express just the epitopes of choice eliminating unrelated or competing epitopes. All of these may be accomplished through techniques well known to those skilled in the art. Techniques for identifying peptides representing important epitopes of the antigen are well known."

Appellant relies upon the disclosure of the instant specification on teaching the skilled artisan to make, formulate and administer full-length antigens, immunologically reactive portions thereof, nucleic acids encoding one or more of those antigen in situ.

However, it is noted this disclosure of the instant specification simply acknowledges the known and general methods of making and using antigens as vaccines at the time the invention was made and does

not provide sufficient direction on how to make and use the breadth of claimed "over represented prostate antigens and immunologically effective portions thereof".

What is missing from appellant's specification as filed are sufficient details as to how to identify or isolate prostate antigens that are "unique" or "substantially unique" to prostate tissues,
given that the objective evidence set forth herein is clear in that the PSA, PAP and PSMA prostate antigens known at the time the invention was made as well as those prostate antigens identified subsequent to appellant's priority date were not uniquely tissue and/or cancer specific.

Again, appellant has not provided sufficient instructions that detail how to make and use "over represented prostate antigens" and "immunologically effective portions thereof" as to relevant structural or functional characteristics that would identify any non-disclosed "over represented prostate antigen" or "immunologically effective portion thereof" falling within the scope of the claimed inventions, including the lack of disclosure in the specification as filed with respect:
to the structure of "over represented prostate antigens" other than references to the known sequences of PSA, PAP and PSMA (no sequences disclosed in the specification as-filed),
to the appropriate HLA for selecting candidate peptides,
to the appropriate in vitro or in vivo assays or endpoints (e.g. proliferation, DTH, CTLs) and

nor has appellant addressed
that the low level of immunogenicity of selected candidate peptides from prostate antigens likely reflects the biological reality of the molecule rather than any deficiency with the assay system employed
and there is still no conclusive data that immunogenicity in vitro strongly correlates with clinical benefit in vivo.

The specification does not provide even a sufficient starting point for screening or testing for such "over represented prostate antigens" and "immunologically effective portions thereof", including "peptides" and "proteins" that "can induce prevention or treatment of prostate cancer",
the instant disclosure does not set forth sufficient procedures that will necessarily lead to discovery or identification for such "over represented prostate antigens" and "immunologically effective portions thereof" and
it does not identify suitable members other than the full-length PSA, PAP and PSMA prostate antigens known by the skilled artisan at the time the invention was made to provide a sufficient number of species to support the claimed "genuses" by providing sufficient disclosure to teach those of ordinary skill in the art how to make and use the claimed as broadly as it is claimed in the subject matter concerning biological materials and reactions in the unpredictable area of prostate cancer required to satisfy the statute, consistent with the decisions by the Federal Circuit and the practice and procedures set forth in the MPEP.

Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.
See Genentech, Inc. v. Novo Nordisk A/S 42 USPQ2d 1001, 1005 (Fed. Cir. 1997) quoting In re Wright, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

The application does no more than describe the desired expression and function of the claimed "genuses" broadly encompassed by the claimed invention and does not contain sufficient information by

which a person of ordinary skill in the art would understand that the inventors have enabled the claimed "over representative prostate antigens" and "immunologically effective portions thereof", as broadly encompassed by the claimed invention.

In view of the lack of predictability of the art to which the invention pertains and the lack of established clinical protocols for effective cancer vaccines and prostate cancer therapies; undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed products and methods are effective for establishing protective anti-tumor responses.

Rejection Under 35 U.S.C. § 112, Second Paragraph, Indefiniteness

Claims 1, 2, 4-8, 10-15, 17-22, 24-28, 30-34, and 37-40 are indefinite in the recitation of "over represented antigens" because the term "over represented" is a relative term which renders the claims indefinite. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

At the time the invention was made,
Cancer Principles & Practice of Oncology, 4th Edition, edited by DeVita et al., J.B. Lippincott Company, Philadelphia, 1993 (See Chapter 35, Cancer of the Prostate on pages 1073-1113 by Hanks et al.) (Hanks et al.)
notes that:

"The two markers of proved clinical utility in the diagnosis and management of carcinoma of the prostate were measurement of levels of PAP and PSA.:
See Markers of the Prostate Cancer on pages 1079-1081 of Hanks et al.

"PAP and PSA are subject to the general constraint for all tumor markers. First, no tumor marker is expressed consistently. PAP and PSA are expressed less in poorly differentiated than in well-differentiated tumor. Histochemical studies typically reveal considerable variation in the expression of both markers from cell to cell within a tumor mass. ... All the factors listed above lead to considerable patient-to-patient variability in marker elevation associated with any given clinical stage and render markers inaccurate staging tools. Finally the correlation between shrinkage of tumor mass and the decline of a marker is not straightforward."
See page 1080, column 1, paragraph 1 of Hanks et al.

"Tumors arising from these cells can manifest PSA- and PAP-positive bladder tumors and PSA-negative PAP-positive rectal carcinoids. In addition, normal axillary and perineal apocrine sweat glands, some apocrine foci in fibrocystic breast disease and apocrine sweat gland carcinomas may stain positive with polyclonal, but not monoclonal anti-PSA antibody. There is a single report of a PSA-producing small cell carcinoma of unknown primary."
See pages 1080-1081, overlapping paragraph of Hanks et al.

About six (6) years subsequent to applicant's filing date of 8/11/93,
Hwang et al. (Seminars in Oncology 26: 192-201 (1999) (Hwang et al.) discuss Prostate Cancer Vaccines: Current Status (see entire document) by stating:

"The paucity of antigens known to be specific for prostate cancer has been a major obstacle to the development of antigen-specific vaccines. The most extensively studied antigens have been PSA and PSMA."
See pages 197-198, overlapping paragraph of Hwang et al.

"While PSA and PSMA have both been shown to stimulate an immune response in vitro, they represent only our "best guess" and may not be true prostate cancer-rejection antigens. An antigen's prevalence, ability to activate T cells and the relative abundance of TCRs specific for each antigen/ MHC complex may define an antigen's ability to prime an immune response. Abundant and potent antigens such as bacterial and viral antigens are thought to hide more "cryptic" antigens, such as tumor and normal tissue antigens. Identification of these true tumor-rejection antigens could provide an avenue for more potent antitumor immunity".
See page 198, column 1, paragraph 2 of Hwang et al.

Similarly, six (6) years later in a reference co-authored by co-inventor Spitler,
in Harris et al., Seminars in Oncology 26: 439 – 447 (1999) (Harris et al.), states that:
PSA, PSMA and PAP were the only targets described that have been identified that could serve as targets for an immune response.
See page 439, column 1, paragraph 2 of Harris et al.

It is noted that Harris et al. refers back to the Hwang et al., Seminars in Oncology reference above as a review of the current status of prostate cancer vaccines.
See page 439, column 2, paragraph 1 of Harris et al. as reference (7).

Therefore, it appears that the PSA, PAP and PSMA were the identified prostate antigens that could serve as targets for an immune response in immunological approaches to the treatment of prostate cancer in the art at the time the invention was made and as well as art about six (6) years subsequent to applicant's filing date of 8/11/93.

Further in the year 2000, seven (7) years subsequent to the filing date of the instant application,
Xu et al. (Cancer Research 60 : 1677 – 1682, 2000) note that the reported prostate markers PAP, PSMA, prostate inhibin peptide, PCA-1, PR92, prostate-associated glycoprotein complex, prostate mucin atigen 12-lipoxygenase and p53 are not entirely tissue and/or cancer specific, hence improved markers are needed for the diagnosis, prognosis and therapy of prostate cancer.
See Introduction of Xu et al.

In addition, Xu et al. note that numerous approaches have been used to dissect the genetic composition of prostate and prostate cancer and that none of the known techniques have provided a complete, systematic and reliable comparison of gene expression between tissue types. Expression cloning using cancer patient serum or T cell lines or clones form patients have identified a panel of genes that may be immunologically relevant, although none have yet been validated and the process is not very efficient.
See Introduction of Xu et al.

Given the lack of tissue and cancer specificity of prostate antigens,
given the variability of expression of even PSA and PAP on prostate tissue,
given the absence of a class of targeted prostate antigens other than the PSA, PAP, and PSMA prostate antigens known at the time the invention was made and for about six (6) years subsequent to the filing date of the instant application and
given the absence of any examples of antigens by which to compare the known PSA, PAP and PSMA prostate antigens;
the metes and bounds of "an over represented prostate antigen" would not be readily apparent to the ordinary artisan at the time the application was filed.

Rejection Under 35 U.S.C. § 103(a), Obviousness

Claims 1-14 and 21-40 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Spitler (U.S. Patent No. 5,738,867) in view of Israeli et al. (U.S. Patent No. 5,538,866), Horoszewicz (U.S. Patent No. 5,162,504), Andriole et al. (Ann. Rev. Med. 42: 9-15, 1991) and in view of art acknowledged methods of delivering antigens of interest to stimulate anti-tumor responses, as disclosed on pages 10-19 of the instant specification and in further evidence of McCarley et al. (Seminars in Surgical Oncology 5:293-301, 1989) alone or as further evidence of Immunology, Second Edition (Kuby, W.H. Freeman and Company, New York, 1991) (see page 590, column 2 and page 613, column 2; Tumor-Associated Antigens and Tumor-Specific Antigens); Fundamental Immunology, Second Edition (Paul, Ed, Raven Press, New York, 1989) (page 931, column 1, paragraph 1; Differentiation Antigens and Other Tumor-Associated Antigens); and Wright et al. (U.S.Patent No. 5,227,471).

Spitler teaches methods of delivering anti-tumor vaccines with tumor associated antigens, including prostate antigens (see Summary of the Invention), as well as known methods of delivering said tumor associated antigens to stimulate anti-tumor responses, encompassed by the claimed invention (see entire document). Spitler teaches that patients with cancer may have the cancer surgically excised and then be given the subject tumor vaccines (see column 10, lines 39-47).

Spitler differs from the instant claimed methods by not disclosing a particular prostate antigen, nor the elected species PSMA per se.

Israeli et al. teach PSMA, including nucleic acids and methods of expressing said PSMA, as well as its expression on prostate tumors (see entire document, including Background of the Invention and Detailed Description of the Invention). Israeli et al. teach that the main metastatic site for prostatic tumor is the bone (column 23, paragraph 2).

Horoszewicz (U.S. Patent No. 5,162,504) teaches that there is a need for monoclonal antibodies which are prostate specific and which do not cross react with other tissue types (see column 6, paragraph 2 and provides for the monoclonal antibodies specific for prostatic tumor antigens and distinguishable from prior prostate antigens (see entire document, including Summary of the Invention and Claims). Horoszewicz further discloses that prostatic epithelium has limited distribution, does not carry out functions vital for the survival of a patient and has been shown to produce organ specific molecules (see column 3, paragraph 3). In addition, the evidence for the selective specificity for the 7E11-C5 for human prostatic epithelium was reinforced by consistently negative results of immunospecific staining of numerous fresh frozen sections from a wide range of human non-prostatic normal or malignant tissues (see column 24, paragraph 3 and Results).

Andriole et al. review the diagnosis and treatment of prostate cancer and teach that surgical excision of the prostate is unsurpassed as a means of controlling organ-confined prostate cancer (see page 13, paragraph 2).

McCarley et al. teach that in prostate cancer, monoclonal antibodies prostate antigens are not usually tumor specific (See Abstract and page 298, column 2, paragraph 3 - page 299).

Pages 10-19 of the instant specification discloses the art known methods of delivering antigens, including tumor associated antigens, such as expression systems and vaccine formulations of interest to stimulate anti-tumor responses encompassed by the claimed methods and vaccines.

Given the teachings of Israeli et al. and Horoszewicz that the PSMA / 7E11 specificity is a marker or antigen for prostate cancer; one of ordinary skill in the art at the time the invention was made would have been motivated to substitute the prostate tumor associated antigen PSMA into the methods and vaccines of stimulating anti-tumor responses, as known and practiced in the prior art, as taught by Spitler and acknowledged by the instant specification as to treat prostate cancer.

Given the tissue and tumor specificity of the PSMA / 7E11 specificity as well as immunogenicity as well as its advantages over previous prostate antigens taught by Israeli and Horoszewicz, coupled with the McCarley et al. teaching that in prostate cancer, monoclonal antibodies prostate antigens are not usually tumor specific (See Abstract and page 298, column 2, paragraph 3 - page 299); one of ordinary skill in the art at the time the invention was made would have been motivated to apply the PSMA prostate antigen in the methods of Spitler to elicit anti-tumor responses to prostate antigens. It would have been obvious to the ordinary artisan to use PSMA in patients with metastatic prostate tumors and/or patients who have had the prostate tumor removed surgically to elicit anti-tumor responses in order to treat said cancer patients.

Again, Spitler teaches that patients with cancer may have the cancer surgically excised and the be given the subject tumor vaccines (see column 10, lines 39-47) and Andriole et al. teach that surgical excision of the prostate is unsurpassed as a means of controlling organ-confined prostate cancer (see page 13, paragraph 2).

Also, it would have been obvious to the ordinary artisan to select portions, particularly extracellular portions of PSMA to stimulate anti-tumor responses. From the teachings of the references and known in the prior art; it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

In further evidence that prostate antigens, including PSMA were considered tumor associated antigens at the time the invention was made, the following is provided.

Immunology, Second Edition (Kuby, W.H. Freeman and Company, New York, 1991) (see page 590, column 2 and page 613, column 2; Tumor-Associated Antigens and Tumor-Specific Antigens) defined tumor associated antigens as follows:

Tumor-associated antigens: cell-surface proteins that are present on tumor cells and normal cells.

Tumor-specific antigens: cell-surface proteins found on tumor cells not on normal cells.

The majority of tumor antigens are not unique to tumor cells but also are present on normal cells and are called tumor-associated antigens. These antigens may be expressed only on fetal cells but not on adult cells, or they may be antigens expressed at low levels on normal cells but at much higher levels by tumor cells. (page 590, column 2).

Fundamental Immunology, Second Edition (Paul, Ed, Raven Press, New York, 1989) (page 931, column 1, paragraph 1; Differentiation Antigens and Other Tumor-Associated Antigens) discloses that some antigens expressed on tumor cells are also expressed on normal cells during at least some stage of differentiation markers. The extent to which these differentiation antigens are expressed by normal cells and tissues can vary from widespread expression to extreme restriction by a small clone of normal cells. Furthermore, the time during development when these markers are expressed on normal cells can vary considerably. Since none of these antigens is tumor specific, they are commonly referred to as "tumor-associated antigens". These antigens represent a very diverse group of glycoproteins and glycolipids

Further, the Background of the Invention on columns 1-2 of Wright acknowledges that PSA, PAP and PSMA (defined as 7E11-C5) were considered tumor associated antigens at the time the invention was made.

In addition, Wright also teaches preparing vaccine formulations of tumor associated prostate antigens for prostate carcinoma, including purified prostate antigen or nucleic acid sequences encoding prostate antigen in vaccine virus (e.g. see columns 12-13, Other Uses, particularly column 12, paragraph 2),

which in turn, is consistent with the teachings of the prior art of record of employing tumor associated prostate antigens in vaccine formulations to treat prostate cancer.

(11) **Response to Argument**

Issue 1: Rejection Under 35 U.S.C. § 112, First Paragraph, Written Description

A. Legal Standard of the Written Description Requirement

Relying upon certain CAFC decision and MPEP § 2163 (II)(A)(3)(a)(ii), appellant argues that the inventor was in possession of the necessary common attributes or features of the elements possessed by members of the genus, providing a measure of predictability for the utility described by the genus.

However, the next line of MPEP § 2163 (II)(A)(3)(a)(ii) states:

For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus.

MPEP § 2163 (II)(A)(3)(a)(ii) also provides the following.

While it is recognized that description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces,

A representative number of species mean that the species are adequately representative of the entire genus. Thus when there is substantial variation within the genus, one must describe the variation within the genus.

MPEP § 2163 (II)(A)(3)(a)(i) provides for the following.

For example, if a strong correlation between structure and function has been accepted in a field of art, one skilled in the art would be able to confidently predict the invention's structure from a detailed description of its function. If there is an accepted correlation between structure and function, the written description requirement may be satisfied through disclosure of function and minimal structure. In the absence of such a correlation, an invention's structure likely will not be inferred from a mere recitation of function and minimal structure.

In this latter case, disclosure of function alone is little more than a wish for possession, It does not satisfy the written description requirement.

For inventions emerging and unpredictable technologies or for invention characterized by factors not reasonably predictable, which are known to one of ordinary skill in the art, more evidence is required to show possession (e.g. disclosure of only a method of making and the function may **not** be sufficient.)

Conception of a compound does not occur unless one has a mental picture of the structure of the chemical or is able to define it by its method of preparation its physical or chemical properties.

It is not sufficient to define it solely by its principal biological property, because an alleged conception having no more specificity than that it is simply a wish to know the identity of any material with that biological property.

The legal standard for written description is met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ... i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

See Enzo Biochem., Inc. v. Gen-Probe Incorporated 69 USPQ2d 1609 (Fed. Cir. 2002).

Further, the Court has interpreted 35 U.S.C. §112, first paragraph, to require the patent specification to "describe the claimed invention so that one skilled in the art can recognize what is claimed. Enzo Biochem, Inc. v. Gen-Probe Inc, 63 USPQ2d 1609 and 1618 (Fed. Cir. 2002). In evaluating whether a patentee has fulfilled this requirement, our standard is that the patent's "disclosure must allow one skilled in the art 'to visualize or recognize the identity of' the subject matter purportedly described." Id. (quoting Regents of Univ. of Cal. v. Eli Lilly & Co., 43 USPQ2d 1398 (Fed Cir. 1997)).

Also, see the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, & 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001 and MPEP § 2163, including those sections indicated above.

To this date, appellant has not provided sufficient evidence that there is or was "a known or disclosed correlation or the sufficiently detailed relevant identifying characteristics" between the structure of the genus of "over represented prostate antigens, "expression systems (comprising encoding nucleic acid or DNA sequences)", "proteins" and "peptides" as broadly claimed and their function "to induce an antitumor immune response for the prevention and treatment of prostatic cancer" (see Administration and Use on page 15 of the instant specification).

Appellant is reminded that the claims are not limited to the prostate antigens PSA, PAP and PSMA known at the time the invention was made,

but rather broadly encompasses any "over represented prostate antigen", "expression system (comprising encoding nucleic acid or DNA sequences)", "proteins" and "peptides" as claimed and

that the "over represented antigen" may be "a protein or a peptide, or peptide fragment of the protein", or may be "a carbohydrate, glycoprotein, lipoprotein or lipid".

See page 6, paragraph 1 of the instant specification.

Again as indicated previously, the rejection under 35 USC 112, first paragraph, written description (as well as enablement) is (are) directed toward the recitation of "over represented prostate antigen", "expression system (comprising encoding nucleic acid or DNA sequences)", "proteins" and "peptides" as broadly claimed and

that the "over represented antigen" may be a "protein or a peptide, or peptide fragment of the protein", or may be a "carbohydrate, glycoprotein, lipoprotein or lipid",

and not on the full-length prostate antigens PSA, PAP and PSMA, known at the time the invention was made.

In contrast, it appears that much of appellant's arguments rely upon the written description of the known prostate antigens, PSA, PAP and PSMA and not on lack of a correlation between the structure and function or the sufficiently detailed relevant identifying characteristics between the structure between the structure and function of the genuses broadly recited in the instant claims.

The specification as filed has not provided sufficient written description of "over represented prostate antigens", including any "protein or a peptide, or peptide fragment of the protein", or may be "a carbohydrate, glycoprotein, lipoprotein or lipid" other than those known prostate antigens at the time the invention was made, namely PSA, PAP and PSMA.

The application does no more than describe the desired expression of an "antigen as being over represented in prostate" and its function "to induce an antitumor response as a vaccine",

but does not contain sufficient information of the correlation between the structure and function or the sufficiently detailed relevant identifying characteristics between the structure between the structure and function

by which a person of ordinary skill in the art would understand that the inventors possessed the claimed invention encompassing "over represented prostate antigens" and "immunologically effective portions thereof", other than PSA, PAP and PSMA prostate antigens, known at the time the invention was made.

Without such "over represented prostate antigens" other than PSA, PAP and PSMA the skilled artisan cannot practice the claimed methods of treatment and vaccines.

It means little to invent a method if one does not have possession of the "over represented prostate antigens" and "immunologically effective portions thereof" that are essential to practice the method. Without possession of the "over represented prostate antigens" and "immunologically effective portions thereof", the claimed endpoints are illusory and there is no meaningful possession of the "methods of inducing antitumor responses" or the "vaccines", as broadly encompassed by the instant claims.

Appellant reliance upon In re Fuetterer and In re Herschler to argue that the patentability of the instant invention lies not in the identification of novel prostate antigens, immunologically effective portions thereof or prostate proteins or peptides, but rather in knowing what to do with prostate antigens that have the disclosed physical and functional characteristics is not consistent with written description requirements.

As the Court has noted, cases such as Herschler indicate that applicant have some flexibility in the mode selected for compliance with the written description requirement,

However, these case do not eliminate the requirement of the patent specification to set forth enough detail to allow a person of ordinary skill in the understand what is claimed and to recognize that the inventor invented what is claimed.

See University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886, 1896 (CAFC 2004).

See the next **Section (B)** for a more complete analysis of the factual determination that there was insufficient written description for the breadth of the claimed invention.

B. Rebuttal

The specification discloses of the genus of over represented antigens and Immunologically effective portions thereof to the person of skill in the art.

Appellant assertions that:

"the specific identity of the prostate antigens used is auxillary to the invention of the claimed methods and compositions beyond the necessary common attribute disclosed"

runs contrary to the requirements of written description requirement under 35 USC 112, first paragraph.

Appellant is reminded that "over represented prostate antigen" and "immunologically effective portions" are claim limitations and are not to be ignored and are not auxillary to the claimed invention.

Again as indicated previously, the rejection under 35 USC 112, first paragraph, written description (as well as enablement) is (are) directed toward the recitation of "over represented prostate antigen", "expression system (comprising encoding nucleic acid or DNA sequences)", "proteins" and "peptides" as claimed and

that the "over represented antigen" may be a protein or a peptide, or peptide fragment of the protein, or may be a carbohydrate, glycoprotein, lipoprotein or lipid",

and not on the full-length prostate antigens PSA, PAP and PSMA.

See page 6, paragraph 1 of the instant specification.

Here, appellant relies upon the identification of the necessary common attribute of these antigens, that they are "overrepresented on normal prostate tissue while also being expressed on malignant prostate tissue".

Appellant also relies upon the "concentration or representation of these antigens is sufficiently higher in normal prostate tissue relative to other normal tissues so that the prostate can be effectively targeted by the immune response raised against this antigen with relative sparring of other organs or tissues"

See page 5, paragraph 2 of the instant specification.

Appellant also relies upon the description of the useful "over represented prostate antigen" though the disclosure of three representative antigens, namely PSA, PSMA and PAP prostate antigens known at the time the invention was made.

Appellant asserts that because the specification clearly leads the skilled artisan to the class of antigens through the specific, necessary physical and functional characteristics and the disclosed examples, the instant specification is sufficient for the claims of Groups I (antitumor methods) and II (vaccines).

In contrast to appellant's assertions that "one of skill in the art would readily recognize that such "an antigen is expressed almost exclusively, i.e. substantially uniquely, on normal prostate tissue at such a level that an immune response elicited against that antigen results in the simultaneous elimination of normal and malignant prostate tissue"

the following from above is noted which provides objective evidence

that the skilled artisan targeted the known PSA, PAP and PSMA prostate antigens at the time the invention, but did not appear to identify a class of tumor associated prostate antigens until years subsequent to appellant's priority date,

that the skilled artisan recognized that even these known prostate antigens PSA, PAP and PSMA were not unique to prostate tissue or to prostate cancer and

that the specification as filed did not provide disclosure of "sufficiently detailed, relevant identifying characteristics ... i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics"

for the class of "over represented prostate antigens" and "immunologically effective portions thereof" broadly encompassed by the claimed invention and asserted by appellant.

The arguments of counsel cannot take the place of evidence in the record. In re Schulze , 145 USPQ 716, 718 (CCPA 1965). See MPEP 716.01(C).

As indicated above the following evidence clearly does not support appellant's assertions that the skilled artisan would readily recognize that such "an antigen is expressed almost exclusively, i.e. substantially uniquely, on normal prostate tissue."

"PAP and PSA are subject to the general constraint for all tumor markers. First, no tumor marker is expressed consistently. PAP and PSA are expressed less in poorly differentiated than in well-differentiated tumor. Histochemical studies typically **reveal considerable variation in the expression of both markers from cell to cell within a tumor mass. ... All the factors listed above lead to considerable patient-to-patient variability in marker elevation associated with any given clinical stage and render markers inaccurate staging tools. Finally the correlation between shrinkage of tumor mass and the decline of a marker is not straightforward."**

See page 1080, column 1, paragraph 1 of Hanks et al.

"Tumors arising from these cells can manifest **PSA- and PAP-positive bladder tumors and PSA-negative PAP-positive rectal carcinoids**. In addition, normal axillary and perineal **apocrine sweat glands**, some **apocrine foci in fibrocystic breast disease** and apocrine sweat gland carcinomas may stain positive with polyclonal, but not monoclonal anti-PSA antibody. There is a single report of **a PSA-producing small cell carcinoma** of unknown primary."

See pages 1080-1081, overlapping paragraph of Hanks et al.

"The paucity of antigens known to be specific for prostate cancer has been a major obstacle to the development of antigen-specific vaccines. The most extensively studied antigens have been PSA and PSMA."

See pages 197-198, overlapping paragraph of Hwang et al.

"While PSA and PSMA have both been shown to stimulate an immune response in vitro, they represent only our "best guess" and may not be true prostate cancer-rejection antigens."

"Identification of these true tumor-rejection antigens could provide an avenue for more potent antitumor immunity".

See page 198, column 1, paragraph 2 of Hwang et al.

Xu et al. note that the **reported prostate markers** PAP, PSMA, prostate inhibin peptide, PCA-1, PR92, prostate-associated glycoprotein complex, prostate mucin antigen 12-lipoxygenase and p53 **are not entirely tissue and/or cancer specific**, hence improved markers are needed for the diagnosis, prognosis and therapy of prostate cancer.

See Introduction on page 1677 of Xu et al.

In addition, Xu et al. note that **numerous approaches** have been used to dissect the genetic composition of prostate and prostate cancer and **that none of the known techniques have provided a complete, systematic and reliable comparison of gene expression between tissue types**. Expression cloning using cancer patient serum or T cell lines or clones form patients have identified a panel of genes that may be immunologically relevant, although **none have yet been validated and the process is not very efficient**.

See Introduction of Xu et al.

Therefore, the facts indicate that the PSA, PAP and PSMA were the tumor associated "prostate antigens" that could serve as targets for an immune response in immunological approaches to the treatment of prostate cancer in the art at the time the invention was made and as well as in the art about six (6) years subsequent to applicant's filing date of 8/11/93 (e.g., see page 439, column 1, paragraph 2 of Harris et al.) and

there does not appear evidence of recognition of a class "over represented prostate antigens" and "immunologically effective portions" that are defined by "sufficiently detailed, relevant identifying characteristics".

To this date, appellant has not provided sufficient direction either to the specification as filed or to the art of the "description or identifying characteristics" of the structure of the "over represented prostate antigens" broadly encompassing any "over represented prostate antigen", "expression system (comprising encoding nucleic acid or DNA sequences)", "proteins" and "peptides" as claimed and

that the "over represented antigen" may be "a protein or a peptide, or peptide fragment of the protein", or may be "a carbohydrate, glycoprotein, lipoprotein or lipid",

other than full-length PSA, PAP and PSMA.

As the evidence indicates,

appellant was not in the possession of a genus of "over represented prostate antigens", other than full-length PSA, PAP and PSMA;

and even with the disclosure of additional prostate antigens seven (7) years subsequent to the 1993 filing date of the instant application, the skilled artisan recognized that these prostate antigens were not entirely tissue and/or cancer specific and

that improved markers were still needed for the diagnosis, prognosis and therapy of prostate cancer.

The instant disclosure as filed did not provide even for one working example of either "a peptide, or peptide fragment of the protein", including "an immunologically effective portion of PSA, PAP or PSMA", as well as "a carbohydrate, glycoprotein and lipoprotein or lipid", other than disclosing references that describe full-length PSA, PAP and PSMA.

In contrast to appellant's assertions,

one of skill in the art would readily recognize that appellant was not in possession of a genus of "prostate antigens that expressed almost exclusively, i.e. substantially uniquely, on normal prostate tissue at such a level that an immune response elicited against that antigen results in the simultaneous elimination of normal and malignant prostate tissue

on the basis of simply disclosing "over represented prostate antigens" as those prostate antigens "overrepresented on normal prostate tissue while also being expressed on malignant prostate tissue" with "the ability to stimulate antitumor immune responses" in the absence of defining the "sufficiently detailed, relevant identifying characteristics" of the genus.

In addition with respect to the claimed limitations of "at least one antigen over represented in the prostate gland and immunologically effective portion thereof" as well as "proteins" and "peptides, the following objective evidence from above is noted.

In reviewing the work of Peshwa et al. (of record), "the selection of candidate peptides that were predictive to be HLA-2 binders were selected and one was chosen for additional study. However, this peptide was weakly immunogenic in vitro, result in moderate cytotoxicity at best and recognition of endogenously synthesized PAP was not strong. **The low level of immunogenicity likely reflects the biological reality of the molecule rather than any deficiency with the assay system employed**."

See page 157, paragraphs 2-3 of Salgaller.

"At first glance it might be disconcerting that so much effort was required to generate what turned out to be a low frequency of in vitro immune reactivity. Yet there is no conclusive data that immunogenicity in vitro strongly correlates with clinical benefit in vivo. In fact, it is interesting that the melanoma antigen MART-1/ MelanA is potently immunogenic in vitro. And yet has produce disappointing clinical results."

See page 160, paragraph 1 of Salgaller.

"Interestingly, the **future direction of many antigen-based prostate cancer vaccines involves the use of proteins rather than peptides**."

See Future Directions on pages 166—167 of Salgaller.

In contrast to appellant's assertions,

the evidence indicates possession or description for "over represented antigens" and "immunologically effective portions and peptides" requires more than mere statements, as disclosed in the instant specification as filed.

As indicated above, the art recognized that the skilled artisan relied upon the knowledge of both the structure of the "over represented prostate antigen" as well as knowledge of the appropriate HLA in order to select candidate peptides and even then, selected peptides by these criteria generated a low frequency of in vitro immune reactivity and not the antitumor immune responses, encompassed by the instant claims.

In contrast, the specification as filed provides for no written description of the structure of "over represented prostate antigens" other than "full-length PSA, PAP and PSMA" and for no written description of "immunologically effective portions and peptides" nor the appropriate HLA in the selection of appropriate candidates that have antitumor functional properties for the claimed invention.

Given that the structures of PSA, PAP and PSMA each are unique and each would be expected to have its own constraints on appropriate "immunologically effective portions and peptides" that met the claimed limitations

and given the lack of correlation between even appropriate candidate peptides and their ability to generate in vitro / in vivo antitumor immune responses,

the skilled artisan would have recognized that appellant was not in possession of sufficient information for the correlation between the structure and function or the sufficiently detailed relevant identifying characteristics between the structure between the structure and function

by which a person of ordinary skill in the art would understand that the inventors possessed the claimed invention encompassing "over represented prostate antigens" and "immunologically effective portions and peptides", other than PSA, PAP and PSMA.

Appellant has not provided sufficient objective evidence that the skilled artisan would be able to identify the claimed "over represented antigens" by a mere assertion or description of a class of over represented prostate antigens that are expressed almost exclusively, i.e. substantially uniquely, on normal prostate tissue at such a level that an immune response elicited against that antigen results in the simultaneous elimination of normal and malignant prostate tissue,

other than simply disclosing that the necessary common attribute of these overpresented prostate antigens is that they are "overrepresented on normal prostate tissue while also being expressed on malignant prostate tissue" and, in turn,

that they can generate effective antitumor immune response in the prevention and treatment of prostate cancer.

An alleged conception having no more specificity than that it is simply a wish to know the identity of any material with that biological property.

Appellant is reminded of their own disclosure and statements concerning the emerging and unpredictable technology or invention of providing cancer vaccines.

As disclosed on page 2, paragraph 1 of the instant specification;

appellant discloses that prostate cancer continues to be refractory to treatment despite many years of efforts to improve therapy. Similarly, appellant discloses that at the time the invention was made; **vaccine development has been slow and no vaccine approved by the FDA for marketing currently exists for any form of cancer**.

As the instant co-inventor Spitler acknowledges,

"Ask practicing oncologists what they think about cancer vaccines and you're likely to get the following response: "cancer vaccines don't work". Ask a venture capitalist or the director of product development at a large pharmaceutical company, and you're likely to get the same response".

See Spitler, Cancer Biotherapy 10:1-3, 1995; page 1, column 1, paragraph 1.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483.

Other than full-length PSA, PAP and PSMA prostate antigens, there is insufficient written description of the claimed "antigen over represented in the prostate gland or an immunologically effective portion thereof" broadly encompassed by the claimed invention. There is a lack of disclosure of sufficient relevant identifying characteristics coupled with a known or disclosed correlation between function and structure of the broadly diverse "over represented prostate antigens" and "immunologically effective portions thereof", including "peptides" and "proteins" recited in the claimed invention other than the full-length PSA, PAP and PSMA prostate antigens at the time the invention was made.

As page 9, paragraph 3 of the instant specification discloses that:

"the invention includes any other antigens that substantially uniquely present on the prostate gland so that prostate derived tissues can be distinguished from other tissue by virtue of the presence of these antigens",

and as page 10, paragraph 1 of the instant specification discloses that:

"antigens useful in the vaccines may be prepared by any suitable methods".

However, what is missing from appellant's specification as filed are sufficient details as to how to identify or isolate prostate antigens that are "unique" or "substantially unique" to prostate tissues,

given that the objective evidence set forth herein is clear in that the PSA, PAP and PSMA prostate antigens known at the time the invention was made as well as those prostate antigens identified subsequent to appellant's priority date were not uniquely tissue and/or cancer specific.

As pages 11-12 of the instant specification discloses:

"Similarly, it may be desirable to express just the epitopes of choice eliminating unrelated or competing epitopes. All of these may be accomplished through techniques well known to those skilled in the art. Techniques for identifying peptides representing important epitopes of the antigen are well known."

Again, appellant has not provided sufficient details as to relevant identifying characteristics of such epitopes or "immunologically effective portions thereof",

such as the structure of "over represented prostate antigens" other than references to the known sequences of PSA, PAP and PSMA (no sequences disclosed in the specification as-filed),

such as the appropriate HLA for selecting candidate peptides,

such as the appropriate in vitro or in vivo assays or endpoints (e.g. proliferation or DTH) and

nor has appellant addressed

that the low level of immunogenicity of selected candidate peptides from prostate antigens likely reflects the biological reality of the molecule rather than any deficiency with the assay system employed

and there is still no conclusive data that immunogenicity in vitro strongly correlates with clinical benefit in vivo.

The specification does not provide even a sufficient starting point for screening or testing for such "over represented prostate antigens" and "immunologically effective portions thereof", including "peptides" and "proteins" that "can induce prevention or treatment of prostate cancer",

the instant disclosure does not set forth sufficient procedures that will necessarily lead to discovery or identification for such "over represented prostate antigens" and "immunologically effective portions thereof" and

it does not identify suitable members other than the full-length PSA, PAP and PSMA prostate antigens known by the skilled artisan at the time the invention was made to provide a sufficient number of species to support the claimed "genuses" by providing "the identifying and distinguishing characteristics" required to satisfy the statute, consistent with the decisions by the Federal Circuit and the practice and procedures set forth in the MPEP.

The application does no more than describe the desired expression and function of the claimed "genuses" broadly encompassed by the claimed invention and does not contain sufficient information that correlates structure (versus expression) and function (antitumor responses in the absence of information on appropriate HLA interactions, in vitro and in vivo assays and endpoints) by which a person of ordinary skill in the art would understand that the inventors possessed as broadly encompassed by the claimed invention.

Based on mere statements, the skilled artisan cannot practice the claimed methods of treatment and vaccines.

It means little to invent a method if one does not have possession of the claimed "antigen over represented in the prostate gland or an immunologically effective portion thereof" that are essential to practice the invention.

Without possession of the "over represented prostate antigens" and "immunologicallay effective portions thereof", the claimed endpoints of "inducing an antitumor immune response in a potential or actual prostate tumor-bearing subject" and "vaccines for eliciting an antitumor immune response to prostate tumors" are illusory and there is no meaningful possession of the claimed inventions.

Appellant has not provided sufficient written description of the "correlation between structure and function" of the scope of "over represented prostate antigens" and "immunologically effective portions thereof", including "peptides" and "proteins" that can "induce prevention or treatment of prostate cancer", broadly encompassed by the claimed invention.

As provided for by the MPEP § 2163 (II)(A)(3)(a)(i) and the Legal Standard of Written Description above.

In the absence of such a correlation, an invention's structure likely will not be inferred from a mere recitation of function and minimal structure.

In this latter case, disclosure of function alone is little more than a wish for possession, It does not satisfy the written description requirement.

For inventions emerging and unpredictable technologies or for invention characterized by factors not reasonably predictable, which are known to one of ordinary skill in the art, more evidence is required to show possession.

It is not sufficient to define it solely by its principal biological property, because an alleged conception having no more specificity than that it is simply a wish to know the identity of any material with that biological property.

Appellant's arguments are not found persuasive

C. Rebuttal

Neither Fiers, Fiddes, nor Eli Lilly are applicable to the instant invention.

Appellant further asserts that the holdings of Fiers, Fiddes and Eli Lilly are distinct from the instant invention because the claimed inventions in each of these cases is a novel DNA sequence while the instant claims involved using protein and DNA sequence when the patentability of the method lies in the method itself, not in a particular protein or DNA sequence.

In contrast to appellant's unsupported position and distinctions between DNA and the general applicability of the written description requirement under 35 USC 112, first paragraph, the Court does not distinguish between product claims and method claims with respect to written description.

"Regardless whether a compound is claimed per se or a method is claimed that entails the use of the compound, the inventor cannot lay claim to that subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds or infringing methods from non-infringing methods". See Univ. of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886, 1894 (CAFC 2003).

Neither the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday January 2001, nor MPEP 2163 stand for limiting the written description requirement under 35 USC 112, first paragraph, to DNA claims to the exclusion of other products and any process claims.

Appellant's arguments have not been found persuasive.

Issue 2: Rejection Under 35 U.S.C. § 112, First Paragraph, Enablement

A. Legal Standard of the Enablement Requirement

In addition to appellant's recitation of the legal standards of enablement, the following is noted.

The Federal Circuit has repeatedly held that the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.

In re Wright, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Also, see MPEP 2164.08.

The amount of guidance or direction need to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art.

In re Fisher, 166 USPQ 18, 24, (CCPA 1970). Also, see MPEP 2164.03.

"A recurring problem is whether a specification that sets forth a single or a limited number of examples can be enabling of broad claims when the subject matter concerns biological materials or reactions which are generally considered to be unpredictable."

Enzo Biochem Inc. v. Calgene Inc. 52 USPQ2d 1129, 1138 (CAFC 1999).

The enablement determination is made by looking back to the filing date of patent application and determining whether undue experimentation would have been required to make and use claimed invention at that time and since factors if applied from proper temporal perspective and useful methodology for determining enablement.

Enzo Biochem Inc. v. Calgene Inc. 52 USPQ2d 1129 (CAFC 1999).

Given the relative incomplete understanding in the biotechnological field involved, and the lack of a reasonable correlation between the narrow disclosure in the specification and the broad scope of protection sought in the claims, a rejection under 35 USC 112, first paragraph for lack of enablement has been appropriate. Also see MPEP 2164.08.

Breadth of Claims: Predictability / Unpredictability of the Art
Quantity of Experimentation Necessary to Practice Prostate Cancer Vaccines and Immunotherapy

Cancer vaccines, including, Prostate Cancer Vaccines and Immunotherapy have been a highly unpredictable art which is amply supported by the evidence. It is important to realize that cancer vaccines, including prostate cancer vaccines and immunotherapy have not been straightforward or as easy to apply as was initially hoped, nor has the interpretation of results been unambiguous and has led to their dismissal in certain instances.

The amount of experimentation required to adapt the practice of prostate cancer immunotherapy has been quite high, with a number of failed attempts, including appellant's own efforts.

In the absence of objective evidence to the contrary, it appears that the PSA, PAP and PSMA were the identified tumor associated prostate antigens that could serve as targets for an immune response in immunological approaches to the treatment of prostate cancer in the art at the time the invention was made and as well as art about six (6) years subsequent to applicant's filing date of 8/11/93.

"The paucity of antigen known to be specific for prostate cancer has been a major obstacle to the development of antigen-specific vaccines. The most extensively studied antigens have been PSA and PSMA."

See pages 197-198, overlapping paragraph of Hwang et al.

"While PSA and PSMA have both been shown to stimulate an immune response in vitro, they represent only our "best guess" and may not be true prostate cancer-rejection antigens."

See page 198, column 1, paragraph 2 of Hwang et al.

Further in the year 2000, seven (7) years subsequent to the filing date of the instant application,

Xu et al. note that the **reported prostate markers** PAP, PSMA, prostate inhibin peptide, PCA-1, PR92, prostate-associated glycoprotein complex, prostate mucin antigen 12-lipoxygenase and p53 **are not entirely tissue and/or cancer specific**, hence improved markers are needed for the diagnosis, prognosis and therapy of prostate cancer.

See Introduction of Xu et al.

In addition, Xu et al. note that **numerous approaches** have been used to dissect the genetic composition of prostate and prostate cancer and that **none of the known techniques have provided a complete, systematic and reliable comparison of gene expression between tissue types**. Expression cloning using cancer patient serum or T cell lines or clones form patients have identified a panel of genes that may be immunologically relevant, although **none have yet been validated and the process is not very efficient.**

See Introduction of Xu et al.

With respect to the lack of predictability of immune responses and antitumor responses in prostate cancer, the following is noted.

"Knowledge of the immune response to prostate cancer has been extremely limited."

See page 193, column 1, first full paragraph of Hwang et al.

"It is important to be aware that immune responses to vaccination do not necessarily imply that the response elicited is against an immunogenic tumor antigen. Furthermore, the magnitude of decreases in PSA levels may not correlate with a clinically meaningful outcome."

See page 593, paragraph 1 of Arlen et al.

"Interestingly, the **future direction of many antigen-directed prostate cancer vaccines** involves the use of **proteins rather than peptides**. Proteins as targets of immunotherapy have several advantages over peptide-based therapeutics including, but not limited to: 1) lack of severe HLA haplotype restrictions (thus making treatment immediately relevant to a larger patient populations), 2) potential helper and adjuvant epitope effects, and 3) lack of need to define the target antigen(s). However, the disadvantages of abandoning peptide-based immunotherapeutics cannot be discounted. **The possibility of generating immune responses to dominant, but clinically irrelevant, heterologous epitopes is one of the major drawbacks."**

See page 166, second full paragraph 2 of Salgaller. See Future Directions.

"Once an overexpressed protein is detected, and its frequency across and within tumor types is established, it appears as though most laboratories are choosing protein-based cancer vaccine as their initial clinical approach. This is most likely because of the **difficulty in defining the precise epitopes responsible for immunogenicity**. The **technologies required to define such epitopes**, among them tandem mass spectroscopy, are **much more difficult and time-consuming than histologically based techniques**."

See page 166, paragraph 3 of Salgaller. See Future Directions.

"As methodologies for the molecular profiling of tumor genes becomes more efficient, e.g. using differential display and microarray analysis, putative markers for prostate cancer have been put forth. It is crucial that the potential immunogenicity of such genes has been established as early as possible. **It is counterproductive to initiate a comprehensive study of a gene whose overexpression may be irrelevant to cancer."**

See page 166, paragraph 4 of Salgaller.

"The development of antigen-specific therapies is hampered by the paucity of information concerning prostate cancer immunology, including the identification, abundance and immunodominance of tumor-associated or –specific prostate cancer epitopes."

"Yet, especially when compared to other carcinomas, much work needs to be done in the realm of understanding the relationship between the immune system and prostate cancer"

See page 167, paragraph 2 of the Salgaller.

In reviewing the work of Peshwa et al. (of record), the selection of candidate peptides that were predictive to be HLA-2 binders were selected and one was chosen for additional study. However, this peptide was weakly immunogenic in vitro, result in moderate cytotoxicity at best and recognition of endogenously synthesized PAP was not strong. **The low level of immunogenicity likely reflects the biological reality of the molecule rather than any deficiency with the assay system employed**.

See page 157, paragraphs 2-3 of Salgaller.

"At first glance it might be disconcerting that so much effort was required to generate what turned out to be a low frequency of in vitro immune reactivity. Yet there is no conclusive data that immunogenicity in vitro strongly correlates with clinical benefit in vivo. In fact, it is interesting that the melanoma antigen MART-1/ MelanA is potently immunogenic in vitro and yet has produce disappointing clinical results."

See page 160, paragraph 1 of Salgaller.

In addition, these published peer-reviewed reports and observations concerning the lack of predictability of inducing antitumor immune responses to any "over represented prostate antigen" or "immunologically effective portion thereof" in the published literature is consistent with appellant's own disclosure and statements concerning the emerging and unpredictable technology or invention of providing cancer vaccines.

As disclosed on page 2, paragraph 1 of the instant specification;

appellant discloses that "prostate cancer continues to be refractory to treatment despite many years of efforts to improve therapy". Similarly, appellant discloses that at the time the invention was made; **"vaccine development has been slow and no vaccine approved by the FDA for marketing currently exists for any form of cancer".**

As the instant co-inventor Spitler (two (2) years subsequent to filing) acknowledges,

"Ask practicing oncologists what they think about cancer vaccines and you're likely to get the following response: "cancer vaccines don't work". Ask a venture capitalist or the director of product development at a large pharmaceutical company, and you're likely to get the same response".

See Spitler, Cancer Biotherapy 10:1-3, 1995; page 1, column 1, paragraph 1.

Furthermore, these published peer-reviewed reports and observations concerning the lack of predictability of inducing prostate tumor immune responses is consistent with the failure of appellant's own clinical trials in providing a clinical benefit to the OncoVaxP™ vaccine, relied upon by appellant to provide sufficient enablement for the breadth of the claimed invention.

In Meidenbauer et al., (The Prostate 43 : 88-100, 2000) (Meidenbauer et al.) (and co-authored by **co-inventor Spitler**), the following observations were made.

"In contrast to the positive ELISPOT assays, we **were unable to detect any killing of PSA-pulsed target in ^{51}Cr-release assays.**"

"Additionally, our date suggest that **PSA-specific T cells consists to a large extent of CD4$^+$ T cells which may not have strong cytolytic activity**."

"We report here, for the first time, that a PSA-based vaccine can generate cellular responses. Most the response were **sustained but at a low level, and in vitro sensitization was necessary to be able to detect postvaccination changes in the frequency of PSA-reactive T cells** in ELISPOT assays.

"Due to the small size of our pilot studies, **no firm conclusions about the clinical efficacy of these treatments are possible.**"

"It appears that larger **studies are warranted to assess the clinical benefit of the vaccine in patients with prostate cancer and to correlate the clinical outcome with immunological endpoints, such as frequency of PSA-responsive T cells**."

See Discussion, particularly page 98, column 2, paragraph 1-2 of Meidenbauer et al.

In McNeel et al. (Immunology Letters 96: 3-9, 2005) (McNeel et al.), the following was noted.

"Spitler and coworkers reported the generation of PSA-specific CD4$^+$ T cells in some subjects treated. No clinical benefit was described, however, and this approach is not being further pursued."

See Protein-based vaccines on page 5, column 1 of McNeel et al.

Amount of Direction or Guidance Presented: Presence of Absence of Working Examples

The amount of direction presented and the lack of working examples provided in the application as filed is very narrow despite the wide breadth of the claims at issue, the unpredictability of prostate cancer immunotherapy and the high quantity of experimentation necessary to practice the breadth of claims.

Other than full-length PSA, PAP and PSMA prostate antigens, there is insufficient through illustrative examples or terminology to teach those how to make and use the claimed "antigens over represented in the prostate gland or an immunologically effective portions thereof" as broadly encompassed by the claimed invention.

As page 9, paragraph 3 of the instant specification discloses that:

"the invention includes any other antigens that substantially uniquely present on the prostate gland so that prostate derived tissues can be distinguished from other tissue by virtue of the presence of these antigens",

and as page 10, paragraph 1 of the instant specification discloses that:

"antigens useful in the vaccines may be prepared by any suitable methods".

As pages 11-12 of the instant specification discloses:

"Similarly, it may be desirable to express just the epitopes of choice eliminating unrelated or competing epitopes. All of these may be accomplished through techniques well known to those skilled in the art. Techniques for identifying peptides representing important epitopes of the antigen are well known."

Appellant relies upon the disclosure of the instant specification on teaching the skilled artisan to make, formulate and administer full-length antigens, immunologically reactive portions thereof, nucleic acids encoding one or more of those antigen in situ.

However, it is noted this disclosure of the instant specification simply acknowledges the known and general methods of making and using antigens as vaccines at the time the invention was made and does not provide sufficient direction on how to make and use the breadth of claimed "over represented prostate antigens and immunologically effective portions thereof".

What is missing from appellant's specification as filed are sufficient details as to how to identify or isolate prostate antigens that are "unique" or "substantially unique" to prostate tissues, given that the objective evidence set forth herein is clear in that the reported prostate antigens, including PSA, PAP and PSMA prostate antigens known at the time the invention was made as well as those prostate antigens identified subsequent to appellant's priority date were not uniquely tissue and/or cancer specific.

Again, appellant has not provided sufficient instructions that detail how to make and use "over represented prostate antigens" and "immunologically effective portions thereof" as to relevant structural or functional characteristics that would identify any non-disclosed "over represented prostate antigen" or "immunologically effective portion thereof" falling within the scope of the claimed inventions, including the lack of disclosure in the specification as filed with respect:

to the structure of "over represented prostate antigens" other than references to the known sequences of PSA, PAP and PSMA (no sequences disclosed in the specification as-filed),

to the appropriate HLA for selecting candidate peptides,

to the appropriate in vitro or in vivo assays or endpoints (e.g. proliferation, DTH, CTLs) and

nor has appellant addressed

that the low level of immunogenicity of selected candidate peptides from prostate antigens likely reflects the biological reality of the molecule rather than any deficiency with the assay system employed

and there is still no conclusive data that immunogenicity in vitro strongly correlates with clinical benefit in vivo.

The specification does not provide even a sufficient starting point for screening or testing for such "over represented prostate antigens" and "immunologically effective portions thereof", including "peptides" and "proteins" that "can induce prevention or treatment of prostate cancer",

the instant disclosure does not set forth sufficient procedures that will necessarily lead to discovery or identification for such "over represented prostate antigens" and "immunologically effective portions thereof" and

it does not identify suitable members other than the full-length PSA, PAP and PSMA prostate antigens known by the skilled artisan at the time the invention was made to provide a sufficient number of species to support the claimed "genuses" by providing sufficient disclosure to teach those of ordinary skill in the art how to make and use the claimed as broadly as it is claimed in the subject matter concerning biological materials and reactions in the unpredictable area of "prostate cancer therapeutic regimens and vaccines" required to satisfy the statute, consistent with the decisions by the Federal Circuit and the practice and procedures set forth in the MPEP.

Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in orde to enable members of the public to understand and carry out the invention.

See Genentech, Inc. v. Novo Nordisk A/S 42 USPQ2d 1001, 1005 (Fed. Cir. 1997) quoting In re Wright, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

The application does no more than describe the desired expression and function of the claimed "genuses" broadly encompassed by the claimed invention and does not contain sufficient information as to how to make and then, in turn, how to how to use the scope of "over representative prostate antigens" and "immunologically effective portions thereof", as broadly encompassed by the claimed invention by which a person of ordinary skill in the art would understand that the inventors have enabled the claimed invention.

The skilled artisan cannot practice the claimed methods of treatment and vaccines based upon mere statements.

It is not sufficient to define "over represented prostate antigen" and "immunologically effective portions thereof' that induce an antitumor immune response in a potential or actual prostate tumor-bearing subject" solely by its principal biological properties of "expression" and "preventing and treating prostatic cancer",

because an alleged conception having no more specificity than that it is simply a wish to know the identity of any material with that biological property.

Appellant's arguments have not been found persuasive.

B. Rebuttal:

The specification supports the breadth of the claimed invention.

In contrast to appellant's assertions that "it is only necessary that the antigens are useful in the methods and compositions and that identifying biochemical information is not required";

again appellant is reminded that "over represented prostate antigen" and "immunologically effective portions" are claim limitations and not to be ignored and are not auxillary to the claimed invention.

In contrast to appellant assertions

that the identifying biochemical information on members of the genus of overrepresented antigens are useful in the claimed methods and compositions is not required for the reasonable enablement of the methods and compositions because the antigens are not defined by biochemical properties, but rather by the "level of expression on normal prostate tissue";

that it is only necessary that the antigens be described in a way that permits the person of skill in the art to identify the class of antigens useful in the methods and compositions, and

that the patentability of the method claims of Group I lies in knowing what to do with the antigen, not in the identification of novel proteins or immunogenic peptides;

the Federal Circuit has repeatedly held that the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.

In re Wright, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Also, see MPEP 2164.08.

As pointed out above with respect to **Rebuttal in the Written Description** rejection, the Court has not distinguished between "method claims" and "products recited in method claims" in terms of compliance with the requirements of 35 USC 112, first paragraph.

"Regardless whether a compound is claimed per se or a method is claimed that entails the use of the compound, the inventor cannot lay claim to that subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds or infringing methods from non-infringing methods".

See Univ. of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886, 1894 (CAFC 2003).

Although appellant relies upon the three prostate antigens PSA, PAP and PSMA that were known at the time the invention was filed and disclosed in the specification as filed and several Declarations to show that a particular PSA-based vaccine (OncoVAxP™) was able to generate anti-PSA responses to support the enablement of the claimed invention,

appellant is reminded that the claims are not limited to the full-length prostate antigens PSA, PAP and PSMA known at the time the invention was made,

but rather broadly encompasses any "over represented prostate antigen", "expression system (comprising encoding nucleic acid or DNA sequences)", "proteins" and "peptides as well as "immunologically effective portions thereof" as claimed and

that the "over represented antigen" may be "a protein or a peptide, or peptide fragment of the protein", or may be "a carbohydrate, glycoprotein, lipoprotein or lipid".

See page 6, paragraph 1 of the instant specification.

Appellant relies upon the disclosure of a limited number of species of the prostate antigens PSA, PSMA and PAP, that were known at the time the application was filed, and the Spitler declaration under 37 CFR 1.132 and Exhibits to argue that the results of human PSA (OncoVaxP™) to support the in vivo operability and predictability of the claimed invention.

Appellant's reliance and assertions that the routine nature of identifying and using immunogenic peptides is confirmed by the each of the experts in the declarations of record is **clearly inconsistent with the ample objective evidence and scientific explanations in the peer-reviewed publications, including those co-authored by co-inventor Spitler and those addressing prostate-based vaccines, including OncoVaxP™, provided herein.**

See the objective evidence above in the **Legal Standard of the Enablement Requirement** that clearly supports the lack of predictability of immunotherapeutic therapy of prostate cancer, particularly in the absence of sufficient guidance, direction and working examples provided by the instant specification as filed.

Here, appellant attempts to distinguish unique tumor antigens from antigens that are expressed on normal and malignant prostate tissue. Again, it is noted that the majority of tumor antigens are not unique to tumor cells but are also present on normal cells. It is noted that these tumor or tumor-associated antigens (TAAs) may be expressed only during certain limited periods of differentiation on certain cell types or at low levels on certain cell types.

C. Rebuttal

The evidence of record definitely demonstrates the operability of the claimed invention using the guidance provided in the specification.

With respect to reliance upon the Spitler Declaration and the observations based upon OncoVaxP, the following is noted.

Section 4 of Spitler's Declaration indicate that immune responses such as skin test reactivity to PSA, production of IgG antibodies and lymphocyte proliferation to PSA were observed and

while Sections 5 – 10 of Spitler's Declaration asserts that these results are highly indicative of an antitumor effect,

no such observations showing an antitumor effect in patients treated with OncoVaxP appear to be provided.

It is further noted the Sections 3-4 of the Bystryn, Mastrangelo, Oldham and Livingston Declarations indicates that:

"The purpose of the study was to obtain evidence that the vaccines would raise a sufficient cellular immune response to have a beneficial effect with respect to prostate tumors. Such a result could be shown directly be measuring cytotoxic lymphocyte (CTL) generation, however, I am aware that this was not possible in these studies because the assay was not satisfactory because of the lack of an appropriate target cell for the assay".

"The responses measured are understood in the art to be satisfactory substitutes for measuring CTLs".

Appellant asserts that:

"all five patients evidenced a clinical response to the vaccine. In four of the five patients, the disease stabilized (i.e. did not continue to grow), while one showed improvement (i.e. improved bone scan in patient 2). This definitive evidence of the in vivo operability of the claimed invention."

However, the support for these assertions of stabilized disease and improvement in the patients immunized with OncoVaxP™ in the clinical trials of Spitler are not readily apparent in Spitler's Declaration.

The following published references do not support such assertions based on the limited information provided in the Spitler Declaration.

In Meidenbauer et al., (The Prostate 43 : 88-100, 2000) (Meidenbauer et al.) (and co-authored by **co-inventor Spitler**), the following observations were made.

"In contrast to the positive ELISPOT assays, we **were unable to detect any killing of PSA-pulsed target in ^{51}Cr-release assays.**"

"Additionally, our data suggest that **PSA-specific T cells consists to a large extent of CD4$^+$ T cells which may not have strong cytolytic activity**."

"We report here, for the first time, that a PSA-based vaccine can generate cellular responses. Most of the responses were **sustained but at a low level, and in vitro sensitization was necessary to be able to detect postvaccination changes in the frequency of PSA-reactive T cells** in ELISPOT assays.

"Due to the small size of our pilot studies, **no firm conclusions about the clinical efficacy of these treatments are possible**."

"It appears that larger **studies are warranted to assess the clinical benefit of the vaccine in patients with prostate cancer and to correlate the clinical outcome with immunological endpoints, such as frequency of PSA-responsive T cells**."

See Discussion, particularly page 98, column 2, paragraph 1-2 of Meidenbauer et al.

In McNeel et al. (Immunology Letters 96: 3-9, 2005) (McNeel et al.), the following was noted.

"Spitler and coworkers reported the generation of PSA-specific CD4$^+$ T cells in some subjects treated. No clinical benefit was described, however, and this approach is not being further pursued"

See Protein-based vaccines on page 5, column 1 of McNeel et al.

Appellant's assertions that the clinical trials of using the PSA vaccine of Spitler were successful by conferring a therapeutic benefit to the patient are not consistent with the lack of objective evidence of (1) generating CTLs, (2) the generation of low level responses that required in vitro sensitization for detection, (3) the generation of $CD4^+$ T cells which may not have strong cytolytic activity (4) and the lack of clinical benefit in the clinical trials performed by Spitler et al.

With respect to appellant's attempts to distinguish cell-based vaccines from protein-based vaccines, the following is noted.

Appellant attempts to distinguish the cell-based vaccines addressed by Hodge et al. (Int. J. Cancer 63: 231-237, 1995) from the claimed protein-based vaccines is clearly inconsistent with the broader picture of immunotherapeutic strategies and appellant's own acknowledgement and reliance upon whole cell cancer vaccines.

"Immunotherapeutic strategies can be broadly classified into passive therapies and active therapies. Passive immunotherapies include treatment with immunomodulatory agents, infusion of cytokines, or infusion of immune effector agents such as antibodies or lymphocytes. Active immunotherapies include vaccine strategies in which the goal is to elicit host-specific anti-tumor immune responses. Vaccines can be further classified as whole cell vaccines, antigen-specific vaccines and non-antigen-specific vaccines.

See page 4, paragraph 2 of McNeel et al.

In reviewing Immune-based therapies for prostate cancer, McNeel et al. presents Active immunotherapy – vaccines, starting with whole cell vaccines, followed by antigen-specific vaccines and protein-based vaccines.

See Active immunotherapy – vaccines, particularly pages 4-5 of McNeel et al.

Further, generating active anti-tumor immunity against prostate cancer involves generating antitumor immunity via priming a response against appropriate antigens in the right context.

Whole-cell prostate cancer vaccines, including the use of cytokines or adjuvants has been practiced (See pages 197-197 of Hwang et al.)

While whole-cell vaccines have generated much excitement, immunization with tumor-specific antigens have marked the beginning of the next generation of cancer immunotherapy

(See page 197, Antigen-Specific Vaccination of Hwang et al.).

In another review of Therapeutic vaccines for prostate cancer, it is clear that the skilled artisan recognized the use of whole cell vaccines in the treatment of prostate cancer and the advantages of using whole cell tumor cell vaccines in that tumor antigen specific to the patient undergoing therapy would be present in the vaccine.

See Arlen et al., Current Opinion in Investigational Drugs 6: 592 – 596, 2005, particularly page 592, columns 1-2, overlapping paragraph.

Therefore, in contrast to appellant's assertions, attempts at antigen-specific vaccination with tumor-specific antigens has based upon and practiced with whole-cell vaccines.

Appellant asserts that both Ezzell (J. NIH Research 7: 46-49, 1995) and Peshwa et al. (The Prostate 1998) address the limitation of using cellular compositions and therefore are inapplicable to instant invention.

Further, this is a curious position for appellant, including co-inventor Spitler to take;

given the Background Art of the instant specification acknowledges the use of "whole autologous or allogeneic tumor cells" or their extracts in cancer therapy

(See page 2, paragraph 2 of the instant specification)

and

given that Sections 8-9 of Spitler's Declaration in support of the general applicability of the observations of the OncoVaxP vaccine to rely upon various observations performed with "autologous tumor cells"

(See Spitler's Declaration, including Sections 8-9).

With respect to appellant's assertions that Spitler (Cancer Biotherapy 10:1-3, 1995) supports the credibility and the predictability of the claimed invention when read in its entirety,

Spitler describing "active components of vaccines are identified and purified and now available for routine vaccine protocols" still would indicate that identifying and purifying active components is necessary for vaccine protocols.

However, the specification as filed does not appear to identify and purify over represented prostate antigens other than PSA, PSMA and PAP, nor the immunologically effective portions and expression systems broadly encompassed by the claimed methods and vaccines.

"The paucity of antigen known to be specific for prostate cancer has been a major obstacle to the development of antigen-specific vaccines. The most extensively studied antigens have been PSA and PSMA."
See pages 197-198, overlapping paragraph of Hwang et al.

"While PSA and PSMA have both been shown to stimulate an immune response in vitro, they represent only our "best guess" and may not be true prostate cancer-rejection antigens."
See page 198, column 1, paragraph 2 of Hwang et al.

Further in the year 2000, seven (7) years subsequent to the filing date of the instant application, Xu et al. note that the **reported prostate markers** PAP, PSMA, prostate inhibin peptide, PCA-1, PR92, prostate-associated glycoprotein complex, prostate mucin antigen 12-lipoxygenase and p53 **are not entirely tissue and/or cancer specific**, hence improved markers are needed for the diagnosis, prognosis and therapy of prostate cancer.
See Introduction of Xu et al.

In addition, Xu et al. note that **numerous approaches** have been used to dissect the genetic composition of prostate and prostate cancer and that **none of the known techniques have provided a complete, systematic and reliable comparison of gene expression between tissue types**. Expression cloning using cancer patient serum or T cell lines or clones form patients have identified a panel of genes that may be immunologically relevant, although **none have yet been validated and the process is not very efficient.**
See Introduction of Xu et al.

Again, appellant has not identified any "over represented prostate antigen" or "immunologically effective portions thereof", other than full-length PSA, PAP and PSMA, in the specification as-filed and

the art indicates that the lack of predictability of identifying such "antigens" and "immunologically effective portions" that would lead to antitumor immunity, including "inducing antitumor immune responses to prostate cancer".

See the evidence above in the **Legal Standard of the Enablement Requirement** that clearly supports the lack of predictability of immunotherapeutic therapy of prostate cancer, particularly in the absence of sufficient guidance, direction and working examples provided by the instant specification as filed.

"The development of antigen-specific therapies is hampered by the paucity of information concerning prostate cancer immunology, including the identification, abundance and immunodominance of tumor-associated or –specific prostate cancer epitopes."

"Yet, especially when compared to other carcinomas, much work needs to be done in the realm of understanding the relationship between the immune system and prostate cancer"

See page 167, paragraph 2 of the Salgaller.

Again as the co-inventor Spitler (two (2) years after the filing date) acknowledges:

"Ask practicing oncologists what they think about cancer vaccines and you're likely to get the following response: "cancer vaccines don't work". Ask a venture capitalist or the director of product development at a large pharmaceutical company, and you're likely to get the same response".

See Spitler, Cancer Biotherapy 10:1-3, 1995; page 1, column 1, paragraph 1.

Again, these statements by the co-inventor subsequent to the instant priority date in a published article are quite clear in terms of the predictability of cancer vaccines.

Therefore, appellant has recognized the lack of predictability of the nature of the art and state of the prior art to which the instant invention pertains, as similarly disclosed on page 2, paragraph 1 of the instant specification.

Also, the objective evidence clearly indicate that the amount of direction or guidance presented in the specification is limited, and would not permit a person skilled in the art to use the invention without undue experimentation at the time the invention was made.

Appellant's arguments have not been found persuasive.

D. Rebutal.

The evidence of record definitely demonstrates that the person of skill in the art recognizes the disclosure of PSA as enabling for the genus of over represented antigens and immunologically effective portions thereof.

In contrast to the **opinion** Declarations submitted by Bystryn, Mastrangelo, Oldham and Livingston and their reliance upon the limited data of the results of the OncoVaxP™ vaccine in the Spitler Declaration to boldly assert that "analogous vaccines based upon host tissue antigens would behave in a similar manner",

ample objective evidence from peer-reviewed publications stands for quite the opposite positions concerning the predictability of prostate tumor immunotherapy based upon unknown as well as known prostate antigens.

Again, **see the evidence above in the Legal Standard of the Enablement Requirement** that clearly supports the lack of predictability of immunotherapeutic therapy of prostate cancer, particularly in the absence of sufficient guidance, direction and working examples provided by the instant specification as filed.

"The development of antigen-specific therapies is hampered by the paucity of information concerning prostate cancer immunology, including the identification, abundance and immunodominance of tumor-associated or –specific prostate cancer epitopes."

"Yet, especially when compared to other carcinomas, much work needs to be done in the realm of understanding the relationship between the immune system and prostate cancer"

See page 167, paragraph 2 of the Salgaller.

Again, the enablement rejection (as well as the written description rejection) is applied against the breadth of "over represented prostate antigens" and "immunologically effective portions thereof" and not on full-length PSA, PAP and PSMA.

Neither the very limited disclosure of the instant specification as-filed, nor the asserted supporting evidence provide for the predictability of the claimed invention as broadly encompassing any "over represented prostate antigen" or "immunologically effective portion thereof" in compliance with the enablement requirements under 35 USC 112, first paragraph.

Further as noted above, Sections 3-4 of the Bystryn, Mastrangelo, Oldham and Livingston Declarations indicates that:

"The purpose of the study was to obtain evidence that the vaccines would raise a sufficient cellular immune response to have a beneficial effect with respect to prostate tumors. Such a result could be shown directly be measuring cytotoxic lymphocyte (CTL) generation, however, I am aware that this was not possible in these studies because the assay was not satisfactory because of the lack of an appropriate target cell for the assay".

"The responses measured are understood in the art to be satisfactory substitutes for measuring CTLs".

As indicated above, in Meidenbauer et al., (The Prostate 43 : 88-100, 2000) (Meidenbauer et al.) (and **co-authored by co-inventor Spitler**), the following observations were made.

"In contrast to the positive ELISPOT assays, we were **unable to detect any killing of PSA-pulsed target in ^{51}Cr-release assays**."

"Spitler and coworkers reported the generation of PSA-specific CD4^{+} T cells in some subjects treated. No clinical benefit was described, however, and this approach is not being further pursued"

See Protein-based vaccines on page 5, column 1 of McNeel et al.

Therefore, the Declarants' opinion that "the results in the clinical study provide evidence that the vaccines are likely to be effective in exerting a beneficial effect on patients with prostate tumors or at risk for prostate tumors" (see Section 3 of the Declarations) **is clearly inconsistent with the lack of generation of PSA-specific CTLs and the lack of clinical benefit in the clinical trials of Spitler, as evidenced by Meidenbauer et al. and McNeel et al.**

It is noted that the teachings of Berd et al. (J. Clin. Oncol. 15: 2359-2370, 1997), Barth et al. (Cancer Research 54: 3342-3345, 1994), Bystryn et al. (Cancer 69: 1157-1164, 1992) and McCune et al. (Cancer Immunol. Immunother. 32: 62-66, 1990) do not provide for the enablement of prostate cancer immunotherapy, as broadly claimed and as evidenced **above in the Legal Standard of the Enablement Requirement.**

Also, Berd et al. state:

"It is important to note that the magnitude of DTH response to DNP-modified melanoma cells was uniformly high and was **not** predictive of clinical outcome. We believe that the development of cell-mediated immunity to hapten-modified cells is necessary, but **not** sufficient for the generation of an antitumor response."

"Little is known about the importance of dosage schedule for the effectiveness of human tumor vaccines"

See page 2368, column 2, lines 4-11 of Berd et al. (J. Clin. Oncol. 15: 2359-2370, 1997).

Similarly, Bystryn et al. state:

"Our results do **not** allow us to assess the clinical effectiveness of vaccine treatment in patients with melanoma."

See page 1163, column 2, first full paragraph of Bystryn et al. (cancer 69: 1157-1164, 1992).

Further, McCune et al. note that :

"Unfortunately, it has been a long wait for effective immunotherapy. Without effective therapy the test is of **limited value**, but the potential remains"

"The optimal material for tumor antigen skin testing is controversial and far from standardized. This awaits identification and purification of tumor antigens,"

See page 64, column 2, Discussion of McCune et al. (Cancer Immunol. Immunother. 32: 62-66, 1990).

Rather than supporting the predictability of appellant's assertions on the predictability of the breadth of the instant claimed invention based upon the limited observations in the Spitler Declaration on OncoVaxP™,

the objective evidence, including the lack of clinical benefits observed with Spitler's prostate vaccine and the clear limitations described by the asserted supporting references provides a very different conclusion and a conclusion that is consistent with the enablement rejection and not with appellant's bold assertions.

Appellant's arguments have not been found persuasive.

Issue 3: Rebuttal

Claims 1, 2, 4-8, 10-14, 20-22, 24-28, 30-34 and 37-40 particularly point out and distinctly claim the subject matter that appellants regards as the invention.

A. Legal stand of the definiteness requirement.

Appellant's reliance on the MPEP and certain court decisions that "the degree of precision required is one that reasonably apprises the skilled artisan of the scope of the invention and is as precise as the subject matter permits and the use of a relative term fails to automatically render a claim indefinite" is acknowledged.

"A claim is indefinite if its legal scope is not clear enough that a person or ordinary skill in the art could determine whether a particular [product or method] infringes or not." Genevea Pharms., Inc. v. GlaxoSmithKline PLC, 349 F.3d 1373, 1384 (Fed. Cir. 2003).

B. Rebuttal

The specification provides a standard for identifying an antigen as "over represented".

Appellant argues that an expressed teaching of what constitutes an "over represented antigen" is provided on page 5, lines 15-27 of the instant specification, using well known and conventional assessments of therapeutic toxicity.

Appellant submit that the standard for identifying such antigens is plainly defined on page 9, line 21 to page 10, line of the instant specification, which discloses:

"The invention includes any other antigens substantially uniquely present on the prostate gland so that the prostate derived tissue can be distinguished from other tissue by virtue of the presence of these antigens" and the prostate-specific antigens PSA, PAP and PSMA, known at the time of filing.

In addition, it is noted that page 5, paragraph 2 of the instant specification here also defines the term "over represented" in relative terms by disclosing:

"By "over represented" is meant that the concentration of this antigen in prostate is sufficiently higher than its concentration in any other tissue such that the prostate can effectively be targeted by the immune response raised against this antigen with relative sparring of other organs of tissues."

Therefore, the claims stand as being indefinite in the recitation of "over represented antigens" because the term "over represented" is a relative term which renders the claims indefinite. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

The objective evidence indicates that prostate antigens, including those disclosed and known at the time the instant application was filed were not either tissue- or cancer-specific.

"**PAP and PSA are subject to the general constraint for all tumor markers. First, no tumor marker is expressed consistently**. PAP and PSA are expressed less in poorly differentiated than in well-differentiated tumor. Histochemical studies typically reveal **considerable variation in the expression of both markers from cell to cell within a tumor mass. ... All the factors listed above lead to considerable patient-to-patient variability in marker elevation associated with any given clinical stage and render markers inaccurate staging tools. Finally the correlation between shrinkage of tumor mass and the decline of a marker is not straightforward**."

See page 1080, column 1, paragraph 1 of Hanks et al.

"Tumors arising from these cells can manifest **PSA- and PAP-positive bladder tumors and PSA-negative PAP-positive rectal carcinoids.** In addition, normal axillary and perineal **apocrine sweat glands**, some **apocrine foci in fibrocystic breast disease** and **apocrine sweat gland carcinomas** may stain positive with polyclonal, but not monoclonal anti-PSA antibody. There is a single report of a **PSA-producing small cell carcinoma** of unknown primary."

See pages 1080-1081, overlapping paragraph of Hanks et al.

"The paucity of antigens known to be specific for prostate cancer has been a major obstacle to the development of antigen-specific vaccines. The most extensively studied antigens have been PSA and PSMA."

See pages 197-198, overlapping paragraph of Hwang et al.

"While PSA and PSMA have both been shown to stimulate an immune response in vitro, they represent only our "best guess" and may not be true prostate cancer-rejection antigens."

See page 198, column 1, paragraph 2 of Hwang et al.

Further in the year 2000, seven (7) years subsequent to the filing date of the instant application,

Xu et al. (Cancer Research 60 : 1677 – 1682, 2000) note that the **reported prostate markers** PAP, PSMA, prostate inhibin peptide, PCA-1, PR92, prostate-associated glycoprotein complex, prostate mucin antigen 12-lipoxygenase and p53 are **not entirely tissue and/or cancer specific**, hence improved markers are needed for the diagnosis, prognosis and therapy of prostate cancer.

See Introduction of Xu et al.

In addition, Xu et al. note that **numerous approaches** have been used to dissect the genetic composition of prostate and prostate cancer and that **none of the known techniques have provided a complete, systematic and reliable comparison of gene expression between tissue types**. Expression cloning using cancer patient serum or T cell lines or clones form patients have identified a panel of genes that may be immunologically relevant, although **none have yet been validated and the process is not very efficient**.

See Introduction of Xu et al.

Further, the metes and bounds of an "antigen" being "substantially uniquely present" is ambiguous,

given that unique means "being the only one of its kind", and

yet at the same time, the antigen is "substantially" so,

where substantial means "considerable large and significantly large" or "being largely but not wholly what is specified".

See pages 1176 and 1290 of Webster's Ninth New Collegiate Dictionary, Merriam-Webster Inc. Springfield, MA, 1990.

Either something is unique or it is not unique.

How is a "prostate antigen" different from "an over represented prostate antigen" ?

Also, given the expression of all prostate antigens on other tissues or cancers and that this expression on even prostate tissue and cancer is variable, the metes and bounds would not be readily apparent to the ordinary artisan at the time the application was filed.

In addition, there is insufficient evidence that "over represented prostate antigen" was a term of art at the time the invention was made.

Given the lack of tissue and cancer specificity of prostate antigens,

given the variability of expression of even PSA and PAP on prostate tissue,

given the absence of a recognized class of "over represented prostate antigens" other than the tumor associated PSA, PAP, and PSMA prostate antigens known at the time the invention was made and for about six (6) years subsequent to the filing date of the instant application and

given the absence of any examples of antigens by which to compare the known PSA, PAP and PSMA prostate antigens;

the metes and bounds of "an over represented prostate antigen" would not be readily apparent to the ordinary artisan at the time the application was filed.

Issue 4: Rebuttal.

Claims 1-14 and 21-40 are nonobvious.

Appellant assert that this rejection is in error.

Law of the Case:

While the prior art rejection in the instant application has not been decided the BPAI previously, essentially the same prior art rejection has been decided by the BPAI in the grandchild application USSN 09/300,978.

Given the facts are the same or nearly the same in the instant application as the facts in the preceding appeal of USSN 09/300,978,

previously decided points of law should be followed unless overruled and

the application of the law to the particular facts should be consistent from case to case.

The law of the case stands for the principle that issues once decided in a case should not be redetermined.

The law of the case doctrine is limited to issues that were actually decided, either explicitly or by necessary implications, in the earlier litigations.

See Alpha/Omega Ins. Servs. Inc. v. Prudential Ins. Co. of Am. 272 F.3d 176, 179 (5th Cir. 2001) cited by Toro Co. v. White Consolidated Industries Inc., 72 USPQ2d 1449, 1456 (CAFC 2004).

As described in Burke Inc. v. Bruno Independent Living Aids Inc., 51 USPQ2d 1295, 1297 (CAFC 1999);

Rule 47.6(b) state: Opinions and orders which are designated as not citable as precedent ... shall not be employed or cited as precedent. This rule does not preclude assertion of issues of claim preclusion, issue preclusion, judicial estoppel, law of the case or the like based on the a decision of the court rendered in a nonprecedential opinion or order.

Rule 47.6(b) does not unconditionally prohibit citation of nonprecedential opinions but instead permits citation of such opinions for limited purposes.

In this case, the interest of consistency would be ill-served by interpreting Rule 47.6(b) to preclude consideration of affirming the obviousness rejection as a matter of law by the BPAI.

Because the present case concerns essentially the identical issue of law based on essentially the same prior art / factual basis decided by the BPAI in the Decision on Appeal Appeal No. 2004-1185, Application No. 09/300,978, mailed, 2/22/04;

the exception to the non-citation rule should be applied.

The following has been previously pointed out above in **Related Appeals and Interferences Identified** with respect to previously copending USSN 09/300,978.

The Decision on Appeal in USSN 09/300,978 found that:

"Thus, we find no error in the examiner's conclusion that the subject matter of claim 13 on appeal as a whole would have been obvious to a person of ordinary skill in the art the time the invention was made."

See page 8, paragraph 3 of the Decision in USSN 09/300,978.

"Appellants' arguments overlook the broader disclosure in Spitler of using TAAs (tumor associated antigens) in general."

See pages 8-9, overlapping paragraph of the Decision in USSN 09/300,978.

"It is equally clear that immunotherapy of prostatic cancer based upon PSMA would be specific to prostatic tissue whether normal or malignant as discussed in Horoszewicz and Israeli."

See pages 9-10, overlapping paragraph of the Decision in USSN 09/300,978.

"Contrary to appellant's arguments, a joint reading of Spitler, Horoszewicz and Israeli shows that PSMA would be a desirable target."

See page 10, paragraph 2 of the Decision in USSN 09/300,978.

In making arguments concerning that the combination of references relied upon by the examiner was improper,

"appellants do not come to grips with the fact that Spitler itself states that use of an antigen or anti-ids to the antigen will be useful in those vaccine composition."

See page 10, paragraph 3 of the Decision in USSN 09/300,978.

"The decision of the examiner is affirmed."

See page 11, paragraph 3 of the Decision in USSN 09/300,978.

Further it is noted in response to a request for rehearing in USSN 09/300,978.

"We have considered the request for rehearing but the arguments presented are intimately tied to and rely upon Exhibit A – Exhibit D and thus are untimely and inappropriate. We do not find that the request for rehearing points to any argument set forth in the Appeal Brief or the Reply Brief, that we overlooked or misapprehended in reaching our decision of December 22, 2004."

See pages 2-3 of the On Request For Rehearing, mailed 4/25/05 in USSN 09/300,978.

For the record, it is noted that USSN 09/300,978 went abandoned subsequent to the Decision.

Appellant statement, filed 7/25/05, in this application that the consideration of the Decision will be addressed as appropriate in the Reply Brief to the Examiner's Answer is acknowledged.

Further, it is noted that appellant had filed a terminal disclaimer over USSN 09/300,978 in response to the obvious double patenting of record in the instant application.

See Issue 5 in the Brief on Appeal in the instant application.

Therefore, appellant has recognized the obviousness between instant USSN 08/105,444 and USSN 09/300,978.

Therefore, appellant has not provided sufficient reasons or evidence for the Board to depart from the law of the case.

For the convenience of the Board, the following corresponding claims of USSN 09/300,978 and the instant application USSN 08/105,444 are provided for comparison.

Claim 13 of USSN 09/300,978

Claim 13. A method to elicit an antitumor immune response to prostate tumors in a subject, which method comprises administering to said subject at least one active ingredient formulated for administration to said subject, wherein said active ingredient comprises or expresses at least one antigen over-represented in the prostate gland,

wherein said antigen is human prostate-specific membrane antigen (PSMA); or

prostatic acid phosphatase (PAP); or mixtures of the foregoing; or

wherein said active ingredient comprises said at least one antigen or a nucleic acid that generates said antigen or antigens in situ.

Claims 1 - 3 of instant USSN 08/105,444

Claim 1. A method to induce an antitumor immune response in a potential or actual prostate tumor-bearing subject which method comprises administering to said subject a composition comprising an ingredient which is active to induce said immune response and is selected from the group consisting of

at least one antigen over represented in the prostate gland or an immunologically effective portion thereof; and

an expression system capable of generating in situ said antigen.

Claim 2. The method of claim 1 where in said antigen is a protein or peptide.

Claim 3. The method of claim 2 wherein said protein or peptide is selected from the group consisting of prostate specific antigen (PSA), prostate-specific membrane antigen (PSMA), prostatic acid phosphatase (PAP) and an immunologically effective portion thereof.

A. Legal standard of the nonobvious requirement.

Appellant's description of the requirements of a prima facie case of obviousness is acknowledged.

The examiner is not familiar with the nonobvious requirement.

B. Rebuttal.

The cited references cannot properly be combined to result in the claimed inventions.

Appellant submits that the rejection is based upon two assumptions:

(1) the use of cancer-specific antigens to elicit an antitumor response is equivalent to the use of over represented prostate antigens expressed on normal prostate tissue to elicit an antitumor response and

(2) the use of such antigens to generate diagnostic antibodies and passive immunotherapy is commensurate with the use of such antigens to induce an active antitumor immune response.

Once again, appellant's mischaracterizes the rejection of record by asserting assumptions not made and by ignoring the plain reading of the prior art rejection.

The prior art does provide for sufficient motivation and expectation of success in treating prostate cancers with active immunization with tumor-associated antigens (TAAs), including prostate antigens such as PSMA and relying, in part, on co-inventor's Spitler's own prior art.

Also, as pointed out herein, the obviousness rejection has already been adjudicated in copending USSN 09/300,978, wherein the **Board of Appeals has affirmed** essentially the same obviousness rejection as set forth herein, at least with respect to "methods of inducing an antitumor immune response with PSMA, as the "over represented prostate antigen".

1. Rebuttal:

Cancer-specific antigens are not equivalent to the use of prostate-specific antigens expressed on normal tissue.

In contrast to appellant's assertions that Spitler is limited to teaching a "pan-epitope" or "cancer specific antigens" to stimulate a general antitumor immune response to any malignant cell,

Spitler (U.S. Patent No. 5,738,867) teaches methods of delivering anti-tumor vaccines with tumor associated antigens, including prostate antigens (see Summary of the Invention), as well as known methods of delivering said tumor associated antigens to stimulate anti-tumor responses, encompassed by the claimed invention (see entire document).

Still, appellant has not pointed out where Spitler provides such a teaching or such a limited teaching "pan-epitope" or "cancer-specific antigens".

Appellant ignores the prior art teaching of "tumor associated antigens (TAA)" and that PSMA satisfies the criteria of a TAA.

As adjudicated in USSN 09/300,978,

"Appellants' arguments overlook the broader disclosure in Spitler of using TAAs (tumor associated antigens) in general."

See pages 8-9, overlapping paragraph of the Decision in USSN 09/300,978.

Also, in contrast to appellant's lack of acknowledgement that the prostate antigens, PSA, PAP and PSMA (subject to the prior art rejection of record) have been considered **"tumor associated antigens (TAA)"**, the following is noted.

Immunology, Second Edition (Kuby, W.H. Freeman and Company, New York, 1991) (see page 590, column 2 and page 613, column 2; Tumor-Associated Antigens and Tumor-Specific Antigens) defined tumor associated antigens as follows:

Tumor-associated antigens: cell-surface proteins that are present on tumor cells and normal cells.

Tumor-specific antigens: cell-surface proteins found on tumor cells not on normal cells.

The majority of tumor antigens are not unique to tumor cells but also are present on normal cells and are called tumor-associated antigens. These antigens may be expressed only on fetal cells but not on adult cells, or they may be antigens expressed at low levels on normal cells but at much higher levels by tumor cells. (see page 590, column 2).

Fundamental Immunology, Second Edition (Paul, Ed, Raven Press, New York, 1989) (page 931, column 1, paragraph 1; Differentiation Antigens and Other Tumor-Associated Antigens) discloses that some antigens expressed on tumor cells are also expressed on normal cells during at least some stage of differentiation markers. The extent to which these differentiation antigens are expressed by normal cells and tissues can vary from widespread expression to extreme restriction by a small clone of normal cells. Furthermore, the time during development when these markers are expressed on normal cells can vary considerably. Since none of these antigens is tumor specific, they are commonly referred to as "tumor-associated antigens". These antigens represent a very diverse group of glycoproteins and glycolipids.

In further evidence that prostate antigens, including PSMA were considered tumor-associated antigens at the time the invention was made, the following is provided.

The Background of the Invention on columns 1-2 of Wright acknowledges that PSA, PAP and PSMA (defined as 7E11-C5) were considered tumor-associated antigens at the time the invention was made.

Although the prior art does not employ appellant's asserted language of "antigens that are substantially uniquely present on a normal tissue to a degree that that tissue can be distinguished from other normal tissue by virtue of their presence of these antigens" per se,

appellant does not distinguish between PSMA or prostate TAAs and this criteria of "over represented prostate antigens" in the instant claims.

Appellant's arguments have not been found persuasive and are not consistent with the law of the case.

2. Rebuttal:

Because active immunotherapy is separate and distinct from passive imunotherapy, there is no motivation to combine Spitler with Israeli, Horoszewicz, and McCarley.

Appellant argues that it was well known that passive and active immunotherapy are distinct and separate biological processes and therefore the skilled artisan would not consider teachings regarding passive immunotherapy applicable to active immunotherapy.

First of all, appellant has not provided objective evidence to support this asserted lack of applicability of passive to active immunotherapy,

Given both therapeutic regimens often are directed to targeting the same disease to achieve the same therapeutic endpoints, albeit by means and modes of action that differ.

In many instances and as the citation from the text CANCER: PRINICIPLES & PRACTICE OF ONCOLOGY (De Vita et al., eds. 1993) would suggest, one of ordinary skill in the art would have recognized that both passive and active immunotherapeutic approaches to cancer therapy.

As appellant's citation on page 26 of the Brief indicates, passive immunotherapy does not require the active participation of the host immune response, but includes the same effectors (e.g. antibodies and cellular immune responses) as active immunization.

It is acknowledged that active immunization would often be expected to provide longer immunity than passive immunity, passive immunity often provides the use of the same or similar immunologically-based effectors (e.g. antibody or cells of interest).

Therefore in the absence of objective evidence to the contrary, it was readily apparent to one of ordinary skill in the art at the time the invention was made that both passive and active immunotherapy could target the same antigens and the issue was whether the immunotherapeutic strategy relied upon a passive administration of immune effectors or upon the active immunization of the host directly to generate their own immune effectors.

More importantly and to the point of appellant's arguments concerning the lack of teaching of active immunotherapy in the prior art,

it has been noted that appellant acknowledges that Horosewicz's disclosure of active immunotherapy via anti-idiotoypic antibodies.

Although appellant asserts that anti-idiotypic antibodies are a fundamentally different therapy because antigen is not required,

it has been well known in the art that anti-idiotypic antibodies bear an internal image of tumor associated antigens and mimic antigen (e.g. see page 7, paragraph 1 of the instant specification).

Consistent with the Spitler's disclosure in the instant specification,

Spitler (U.S. Patent No. 5,738,867) teaches that their invention may employ either tumor associated antigens or anti-idiotypic antibodies to tumor associated antigens are useful as vaccine-like compounds for the treatment of a variety of cancers (e.g. see column 2, Summary of the Invention).

Therefore, the prior art and the instant application are consistent in recognizing that anti-idiotypic antibodies serve as antigen in the same manner as the antigen itself in active immunization protocols and that ordinary artisan can immunize with the tumor associated antigen or anti-idiotypic antibodies that serve as tumor associated antigens in the treatment of cancer.

Also, it is noted that appellant acknowledges that Horoszewicz teaches active immunization but employs anti-idiotypic antigen rather than antigen, as a fundamentally different therapy. It should be noted that anti-idiotypic antibodies serve as an alternative approach in formulating a vaccine, wherein the anti-idiotypic antibody bears an internal image of the antigen (see page 13, paragraphs 1-2 of the instant specification) (see column 4, lines 24-37 of Spitler). Therefore, anti-idiotypic antibodies serve as alternative to a tumor associated antigen (see page 13, paragraph 2, of the instant specification) (see column 4, lines 24-37 of Spitler; also compare claims 4 and 6 of Spitler). Therefore, tumor associated antigens (TAA) and TAA-specific anti-idiotypic antibodies are alternatives of one another in eliciting active immunization to said TAA.

Note that Spitler is drawn methods and compositions employing liposomes compositions encapsulating or conjugated to tumor associated antigens (TAAs) or anti-idiotypic antibodies to tumor associated antigens (see Summary of the Invention on column 2; also compare claims 4 and 6 of Spitler).

Appellant's arguments appear to be more of form (e.g antigen, anti-id) over substance (e.g., active immunotherapy to prostate antigens to generate antitumor responses).

In addition, Wright also teaches preparing vaccine formulations of tumor associated prostate antigens for prostate carcinoma, including purified prostate antigen or nucleic acid sequences encoding prostate antigen in vaccine virus (e.g. see columns 12-13, Other Uses, particularly column 12, paragraph 2),

which in turn, is consistent with the teachings of the prior art of record of employing tumor associated prostate antigens in vaccine formulations in active immunotherapy to treat prostate cancer.

Here in contrast to appellant's assertions of teaching away by the prior art; there is no discouragement nor skepticism in the prior art for employing a variety of tumor associated antigens from a variety of different tissues to stimulate antitumor responses. Again, the primary Spitler reference is more directed to providing said tumor-associated antigens encapsulated or conjugated to liposomes to achieve effective antitumor responses (see Summary of the Invention).

Consistent with appellant's arguments that the claimed vaccination strategy is fatal for the recipient unless the targeted organ is non-essential, it would have been obvious to the ordinary artisan to use PSMA in patients with metastatic prostate tumors and/or patients who have had the prostate tumor removed surgically to elicit antitumor responses in order to treat said cancer patients. Again, Spitler teaches that patients with cancer may have the cancer surgically excised and the be given the subject tumor vaccines (see column 10, lines 39-47) and Andriole et al. teach that surgical excision of the prostate is unsurpassed as a means of controlling organ-confined prostate cancer (see page 13, paragraph 2). Therefore, the prior art is consistent with appellant's arguments that it would have been expected that the prostate would have been removed in prostate cancer patients and the ordinary artisan would not have been concerned with removing a vital organ. Given the removal of the prostate, the ordinary artisan would not have been concerned with the issued raised by appellant that the elicitation of an immune response to an organ-specific antigen results in the eradication of all antigen-expressing cells whether malignant or not.

In response to appellant's assertions concerning the teachings of tumor associated antigens or organ specific antigens in the context of the primary Spitler reference, the rejection set forth above provide a more thorough review of the meaning and understanding of tumor-associated antigens (TAAs) by the ordinary artisan at the time the invention was made as well as the asserted tumor uniqueness of the disclosed tumor associated antigens in Spitler.

As adjudicated in USSN 09/300,978;

in making arguments concerning that the combination of references relied upon by the examiner was improper,

"**appellants do not come to grips with the fact that Spitler itself states that use of an antigen or anti-ids to the antigen will be useful in those vaccine composition.**"

See page 10, paragraph 3 of the Decision in USSN 09/300,978.

"**It is equally clear that immunotherapy of prostatic cancer based upon PSMA would be specific to prostatic tissue whether normal or malignant as discussed in Horoszewicz and Israeli.**"

See pages 9-10, overlapping paragraph of the Decision in USSN 09/300,978.

"Contrary to appellant's arguments, a joint reading of Spitler, Horoszewicz and Israeli shows that PSMA would be a desirable target."

See page 10, paragraph 2 of the Decision in USSN 09/300,978.

In this case, Spitler teaches methods of delivering antitumor vaccines with tumor associated antigens, including prostate antigens (see Summary of the Invention) and the teachings of secondary references that PSMA was associated with prostate tumors and, in turn, was a targeted prostate tumor antigen would have led one of ordinary skill in the art at the time the invention was made to combine the references to solve a well known problem in the art, namely immunizing individuals with PSMA as a prostate tumor associated antigen in a vaccine to treat prostate cancer.

The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination. In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983). See MPEP 2144.

Given the teachings of Israeli et al. and Horoszewicz that the PSMA / 7E11 specificity is a marker or antigen for prostate cancer; one of ordinary skill in the art at the time the invention was made would have been motivated to substitute the prostate tumor associated antigen PSMA into the methods of stimulating antitumor responses, as known and practiced in the prior art, as taught by Spitler and acknowledged by the specification as to treat prostate cancer. It would have been obvious to the ordinary artisan to use PSMA in patients with metastatic prostate tumors and/or patients who have had the prostate tumor removed surgically to elicit antitumor responses in order to treat said cancer patients.

Appellant's arguments have not been found persuasive and are not consistent with the law of the case.

Issue 5: Terminal Disclaimer has been filed.

Whether the claims are unpatentable under the judicially-created doctrine of obviousness-type double patenting over claims 1-8 of U.S. Patent NO. 5,925,362 and over claims 13, 15,16,28-24 of copending Application Serial No. 09/300,978.

Signed Terminal disclaimers have been submitted and accepted, thereby obviating the obvious double patenting rejection of record.

Given appellant's filing of the terminal disclaimer over USSN 09/300,978, appellant has acknowledged the obviousness between the clams between the two applications and, in turn, acknowledges the applicability of the law of the case with respect to the prior art rejection adjudicated in USSN 09/300,978 to the claims of the instant application USSN 08/105,444.

(13) For the above reasons, it is believed that the rejections should be sustained.

Respectively submitted,

Phillip Gambel, Ph.D.
Primary Examiner
Technology Center 1600
October 31, 2005

Christina Chan
Supervisory Patent Examiner
Art Unit 1644
Conferee

George C. Elliott, Ph.D
Director
Technology Center 1600

Larry Helms, Ph.D.
Supervisory Patent Examiner
Art Unit 1643
Conferee